

# BEST AVAILABLE COPY

WO 02/46472

PCT/US01/46418

phosphate buffer.

621. The method of claim 619 wherein the salt is sodium chloride in a phosphate buffer.

5

622. The method of Claims 599 or 607 wherein the nanoparticles have a diameter ranging between about 10 and about 100 nm.

623. The method of Claims 599 or 607 wherein the nanoparticles have a diameter of about 50 nm.

10

624. The method of Claims 599 or 607 wherein the nanoparticles have a diameter of about 100 nm.

625. The method of Claims 599 or 607 wherein two scattered light detectable nanoparticle probes of different diameters are used.

15

626. The method of claim 624 wherein the nanoparticle probes have a diameter of 50 nm and 100 nm.

20

25

FIG. 1

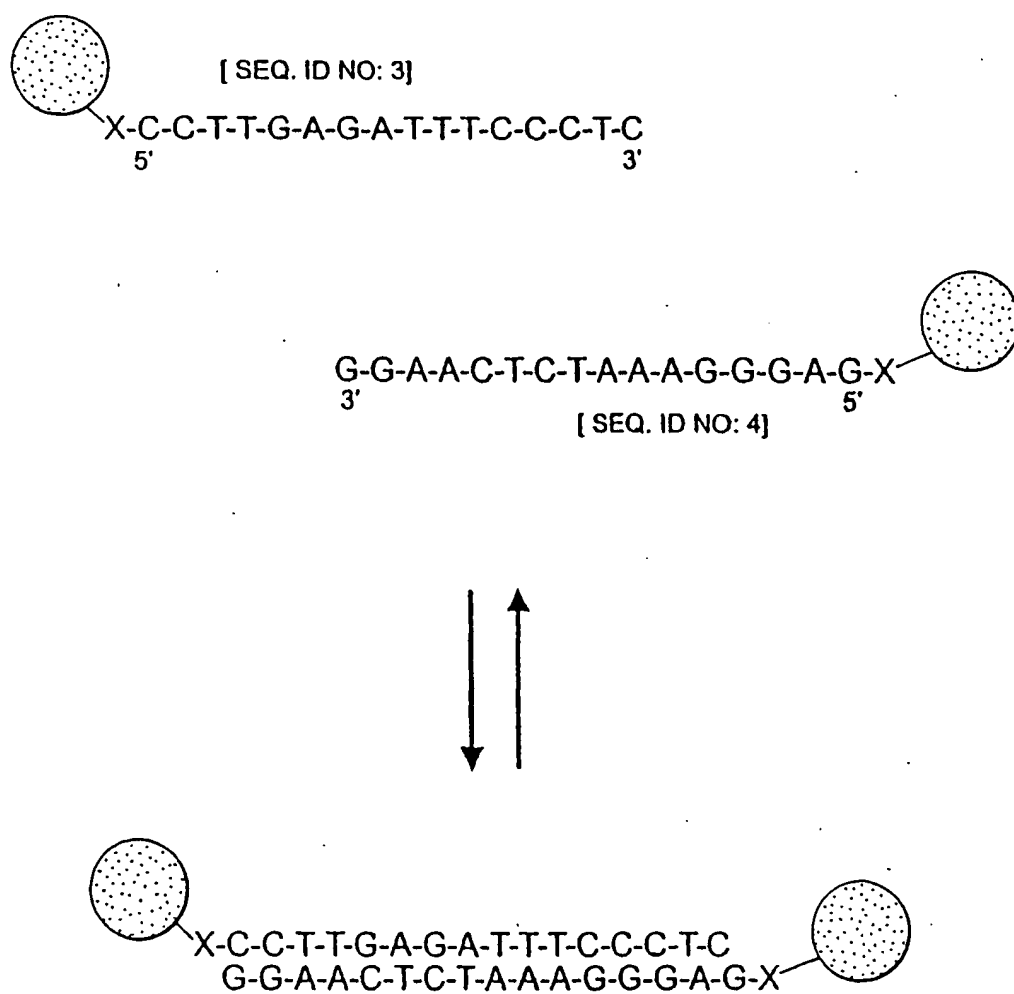


FIG. 2

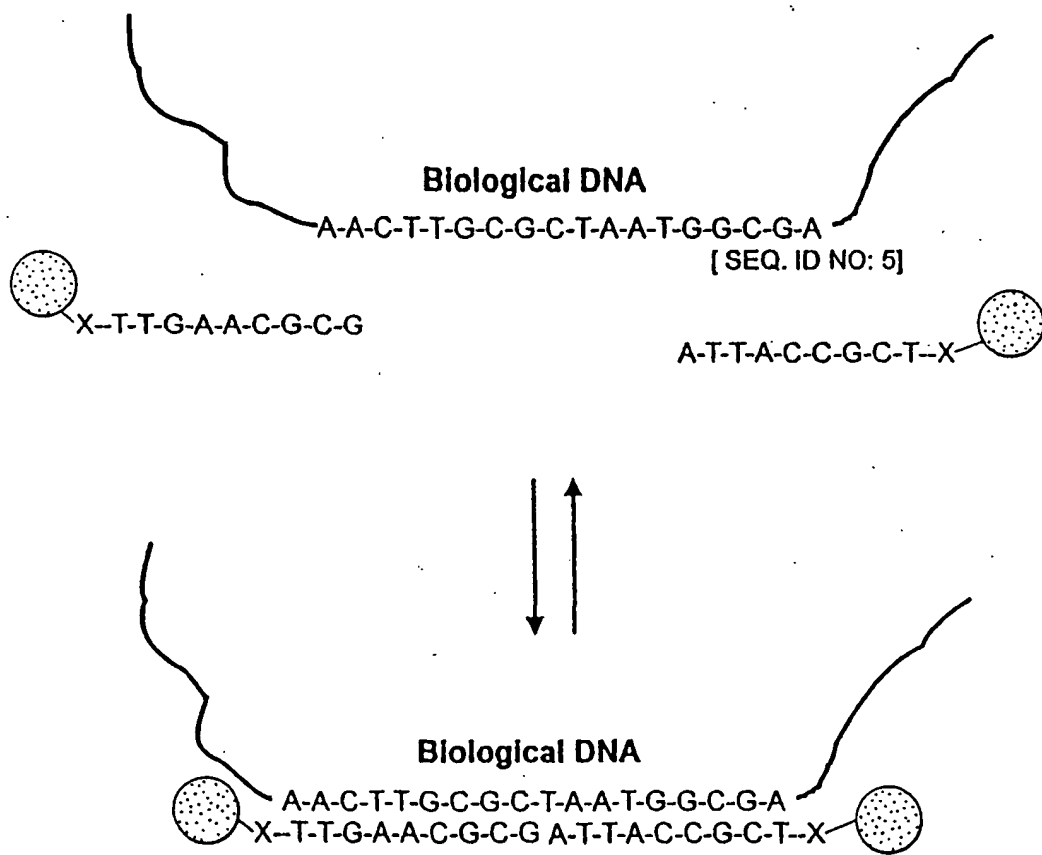
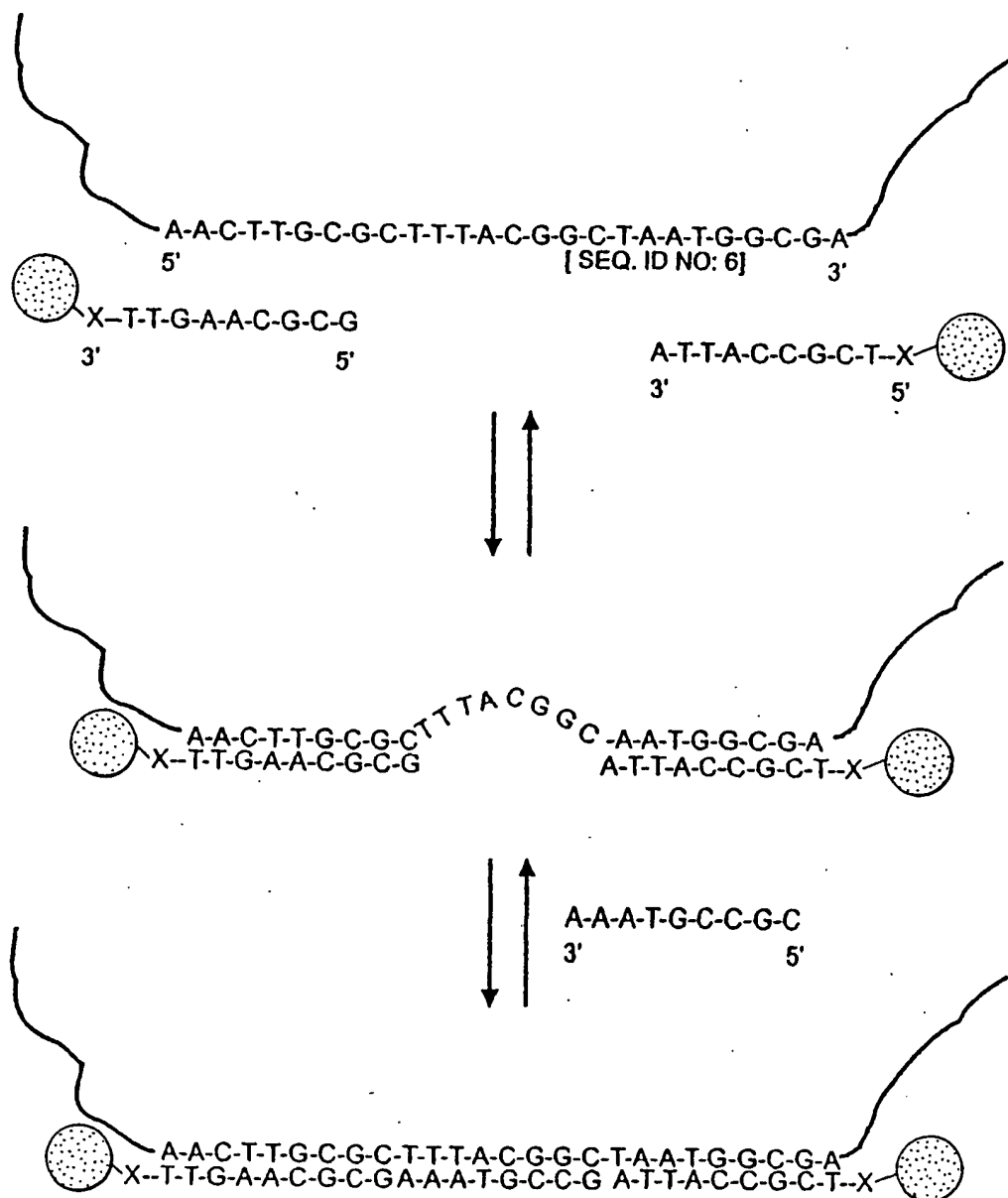


FIG. 3



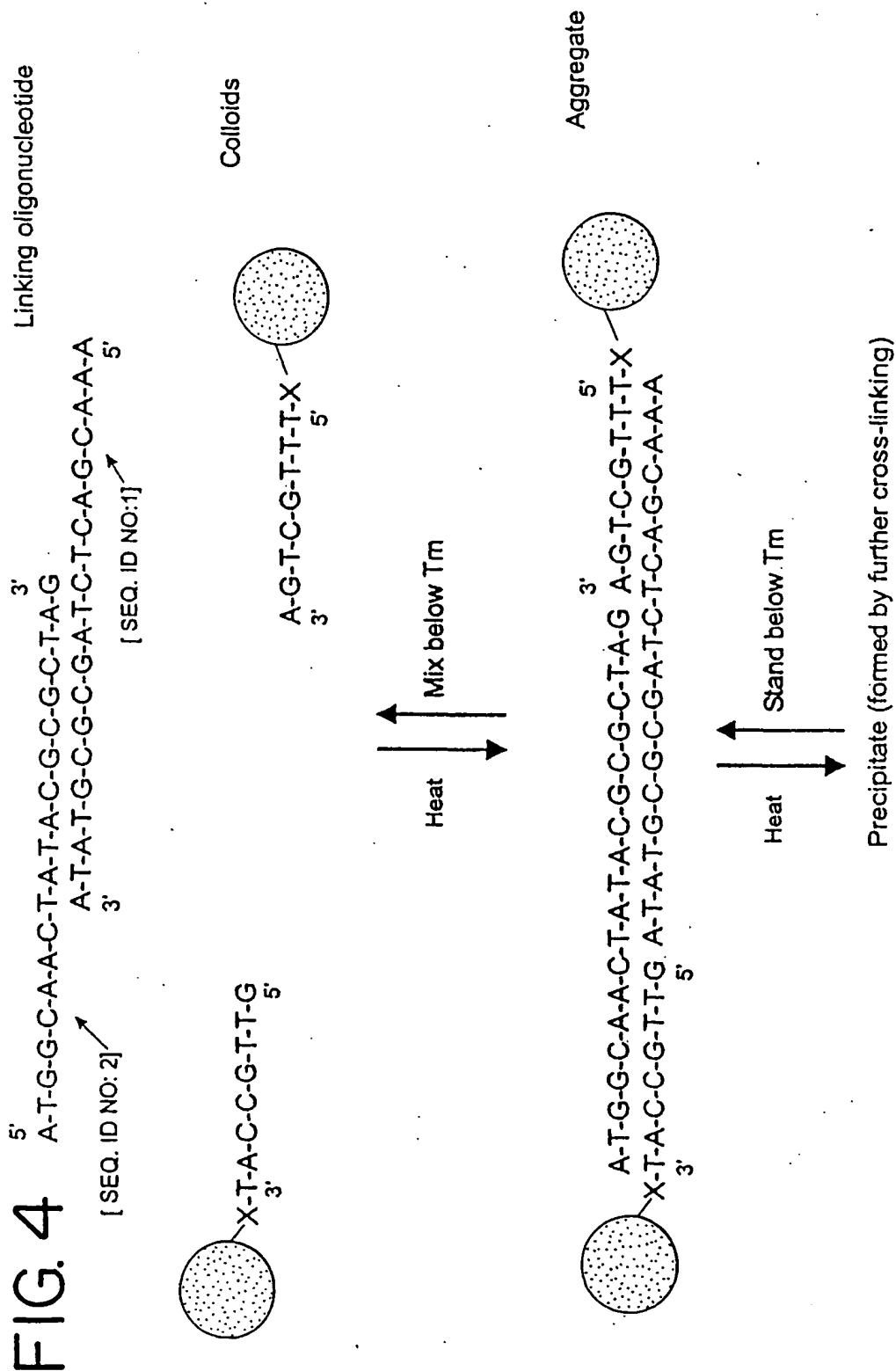


FIG. 5

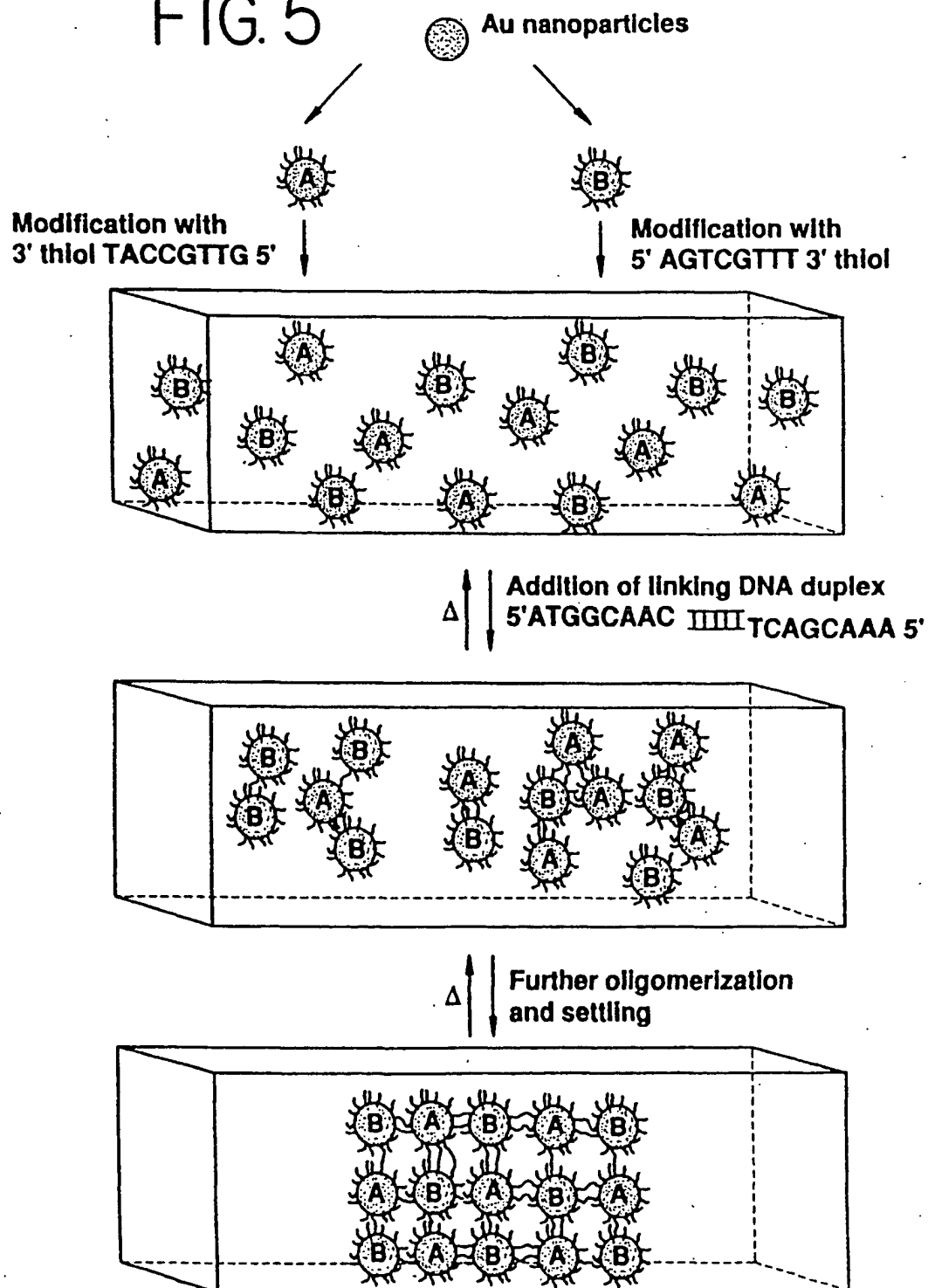
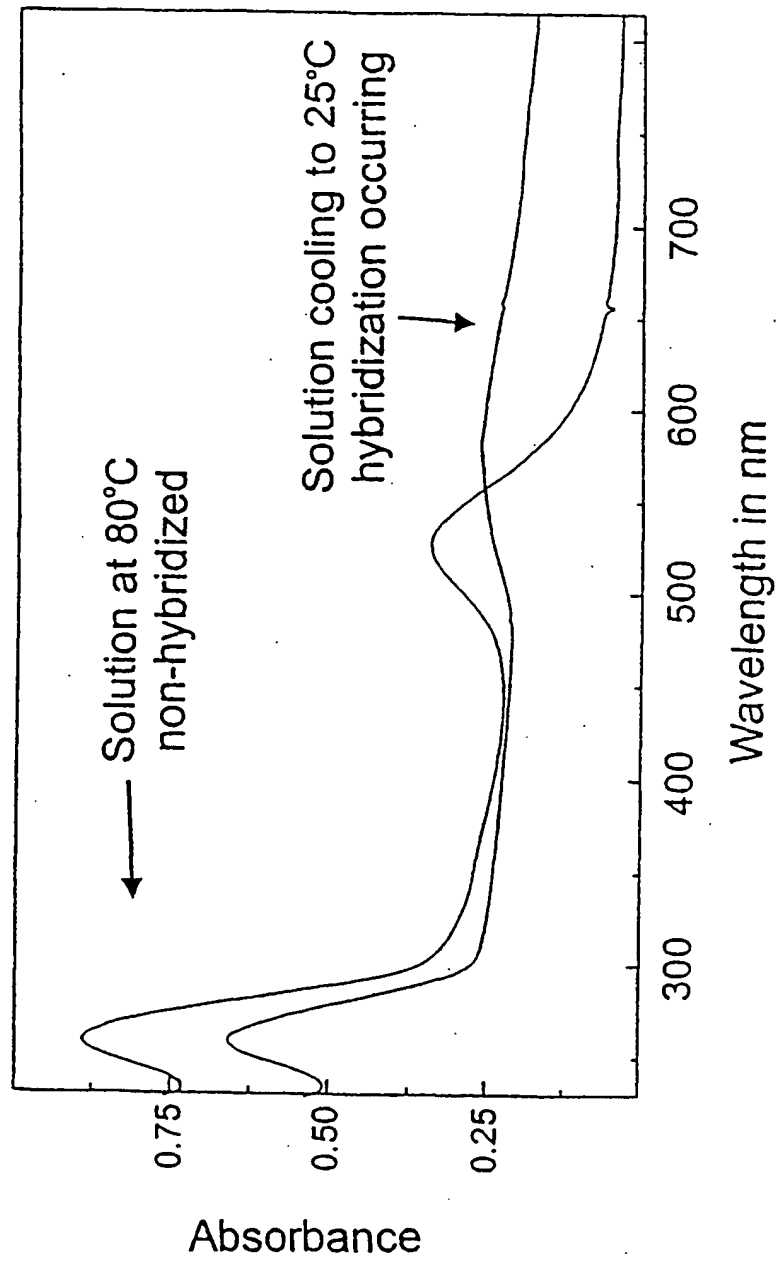


FIG.6A FIG.6B FIG.6C



FIG. 7



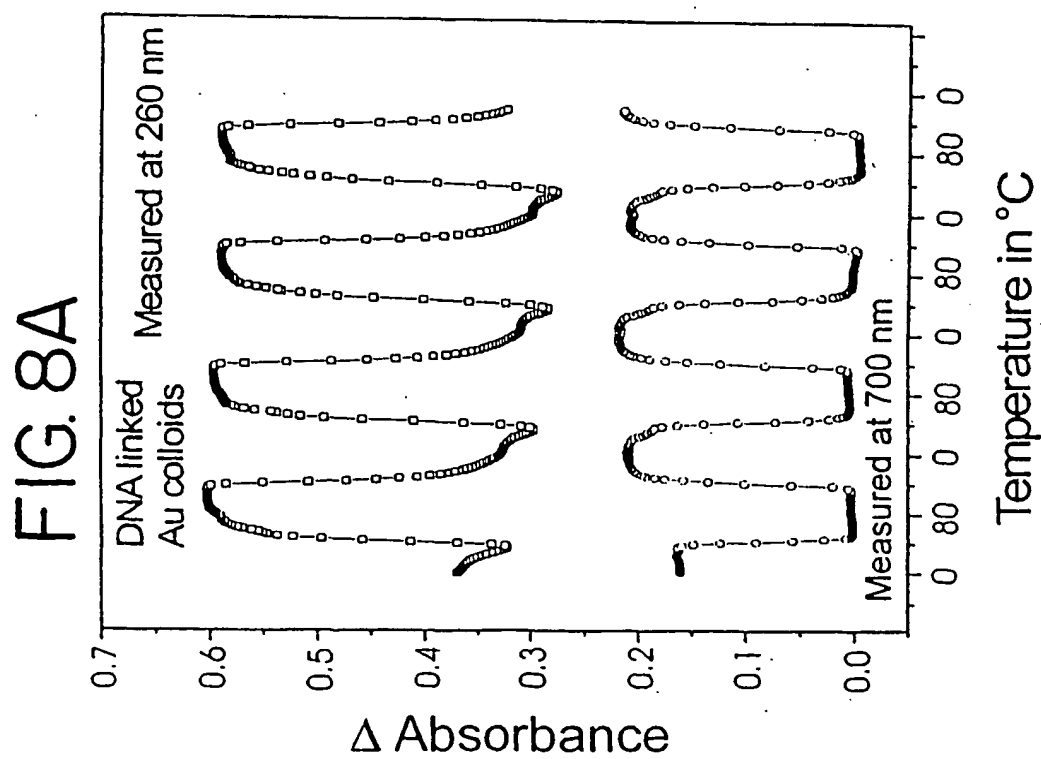
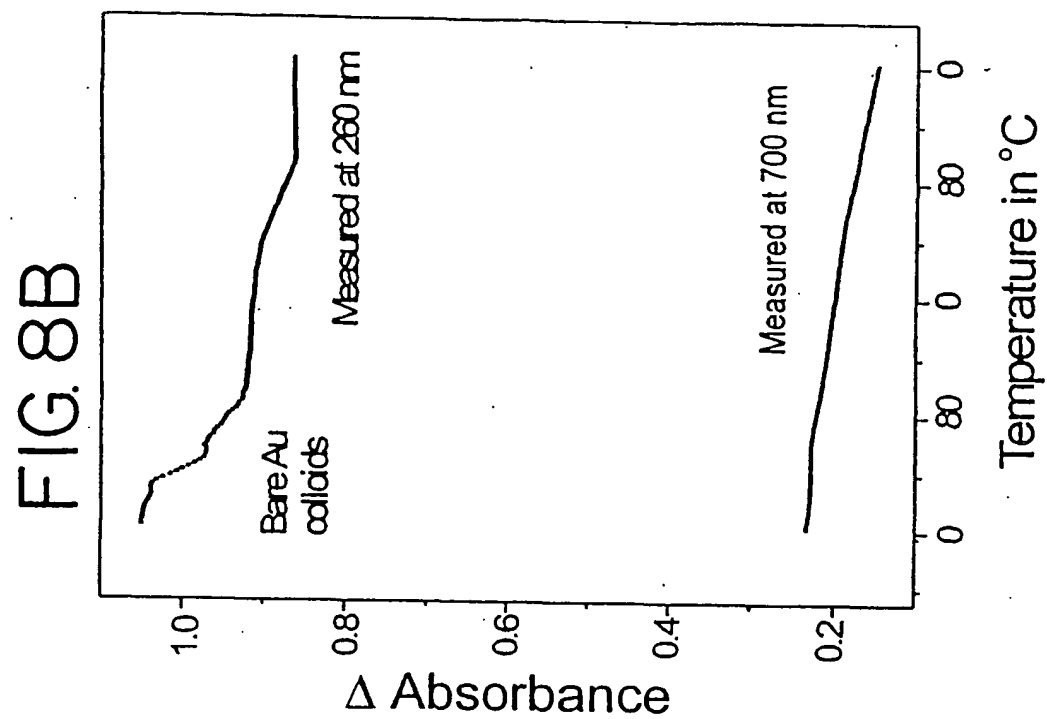


FIG. 9A

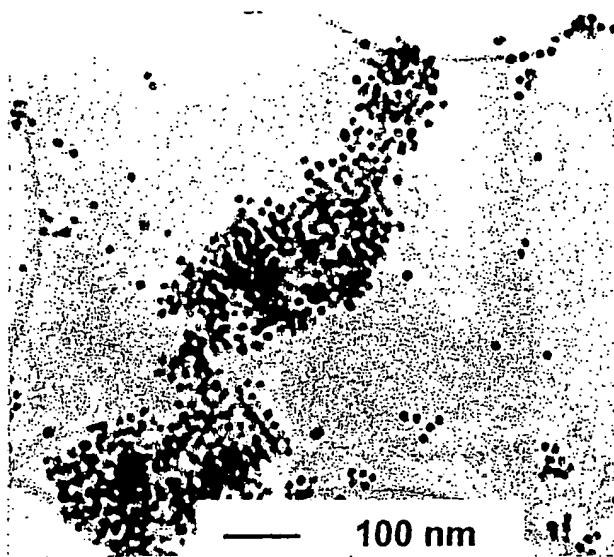


FIG. 9B

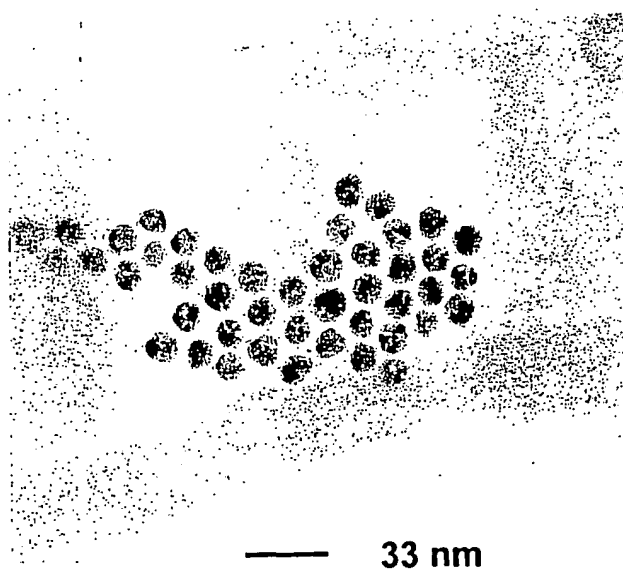
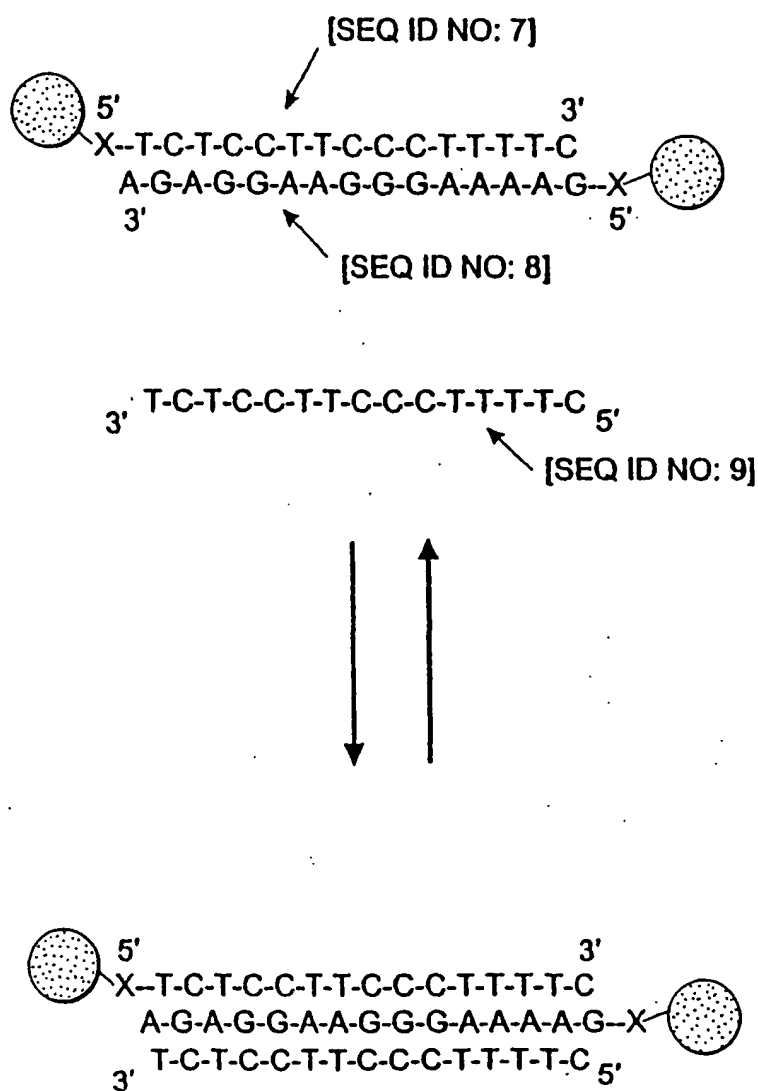
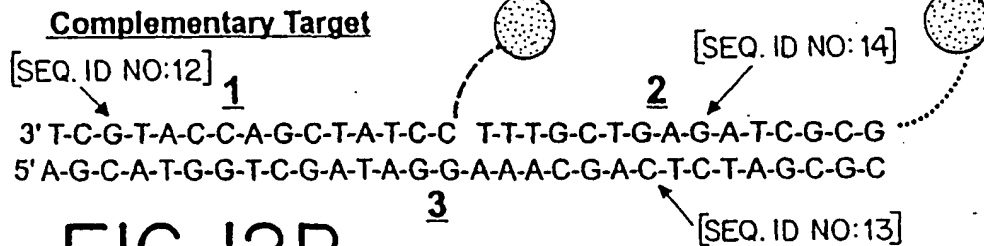


FIG. 10

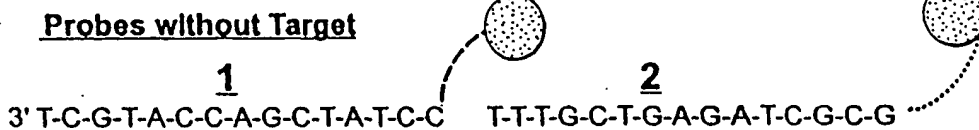




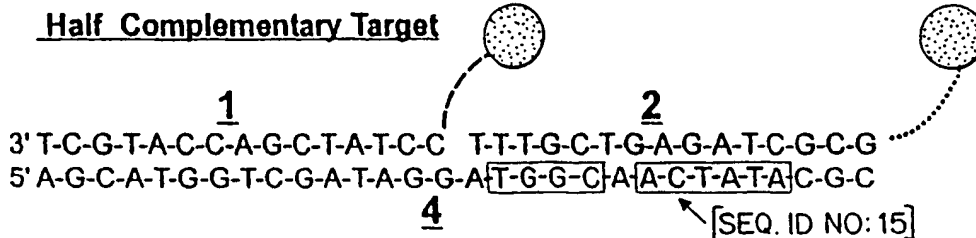
## FIG. 12A



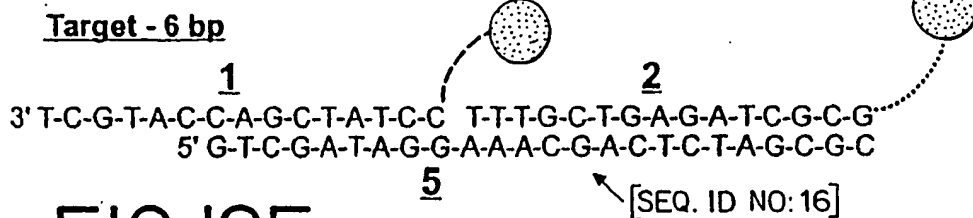
## FIG. 12B



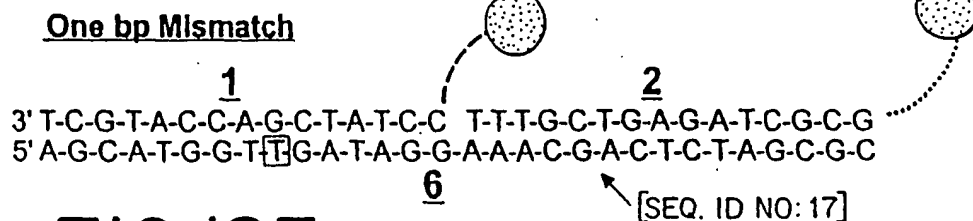
## FIG. 12C



## FIG. 12D



## FIG. 12E



## FIG. 12F

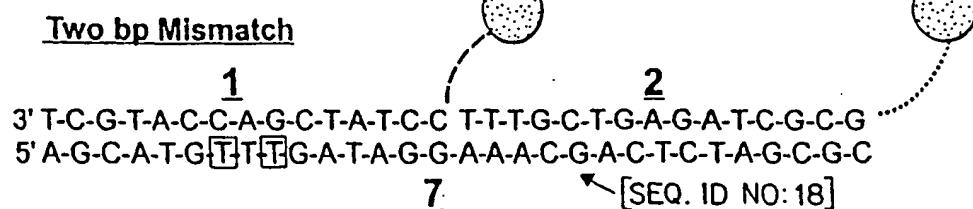


FIG. 13A

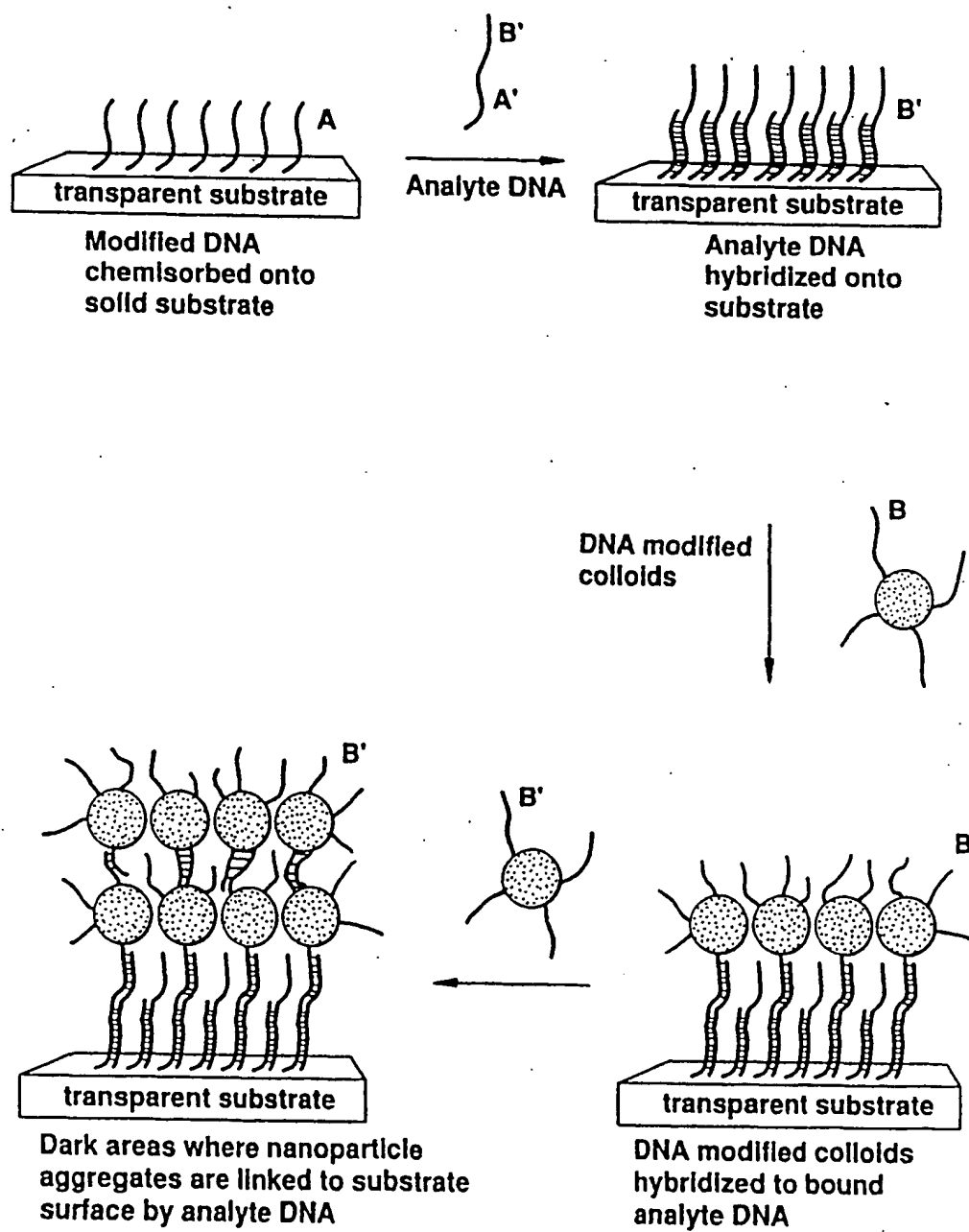


FIG. 13B

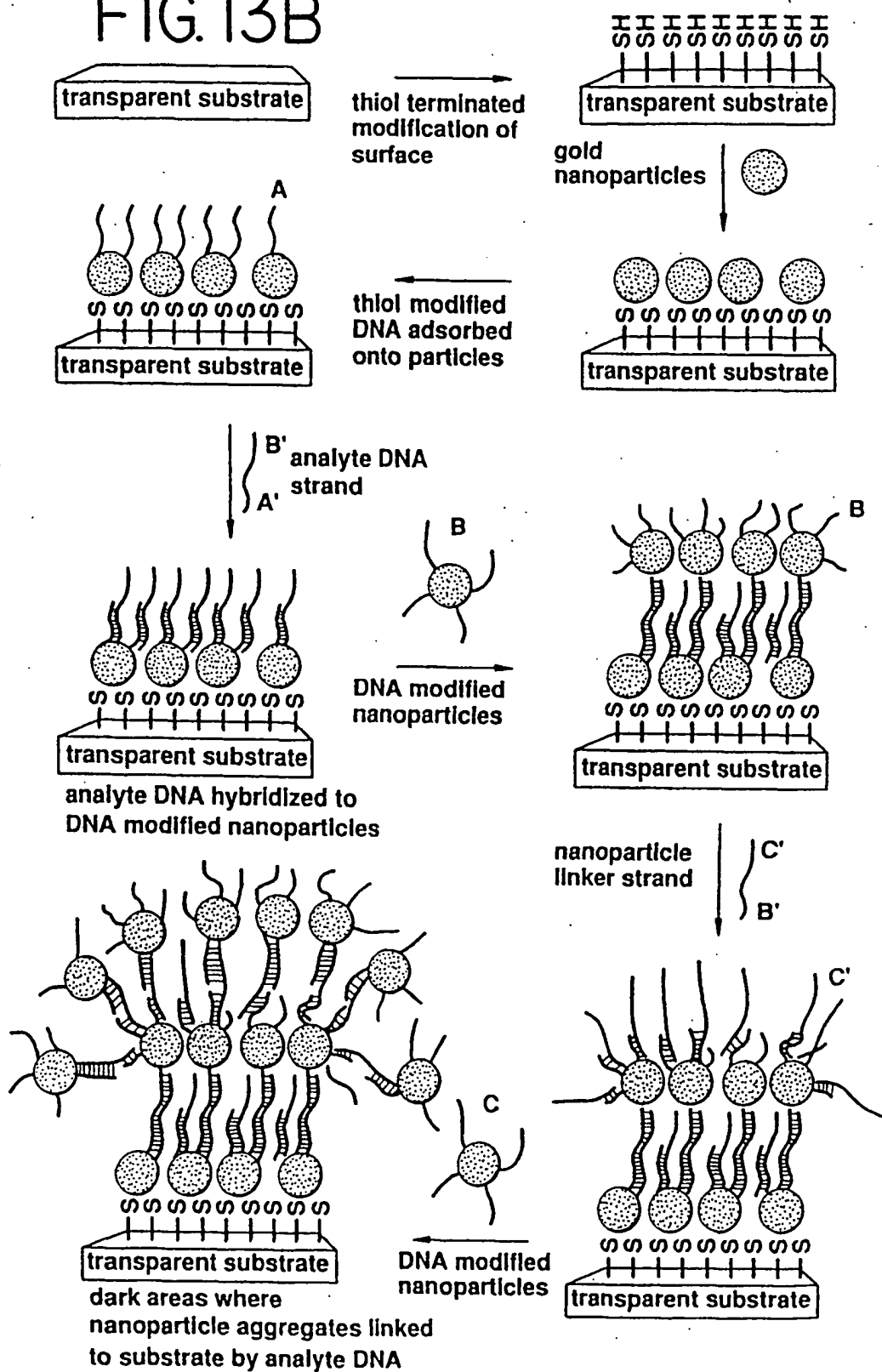


FIG. 14A

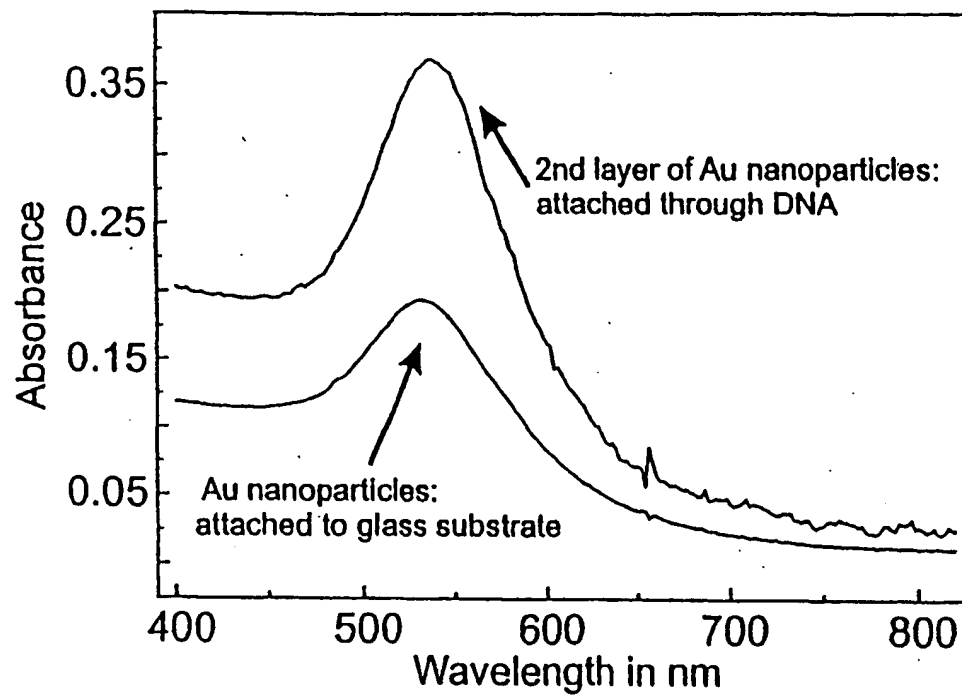


FIG. 14B

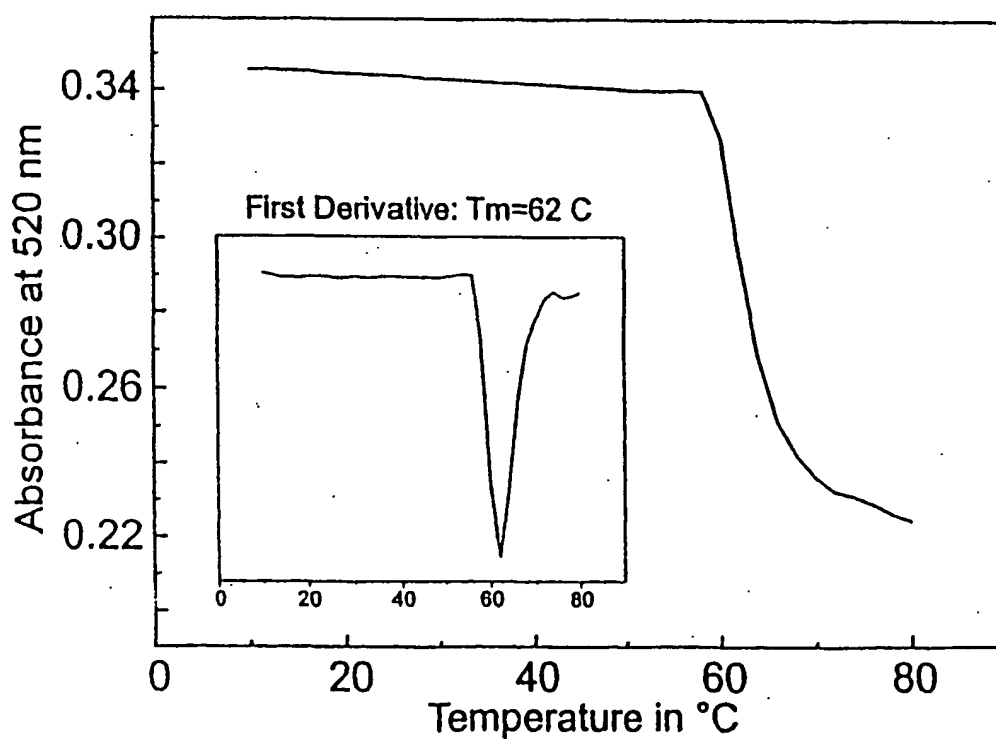


FIG. 15A

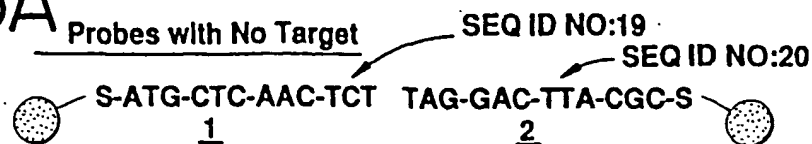


FIG. 15B

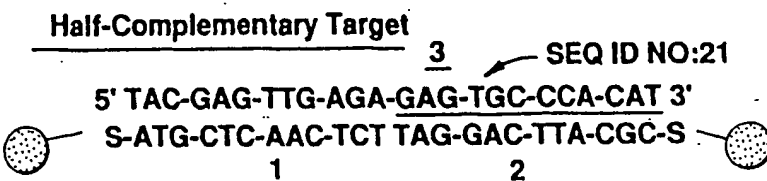


FIG. 15C

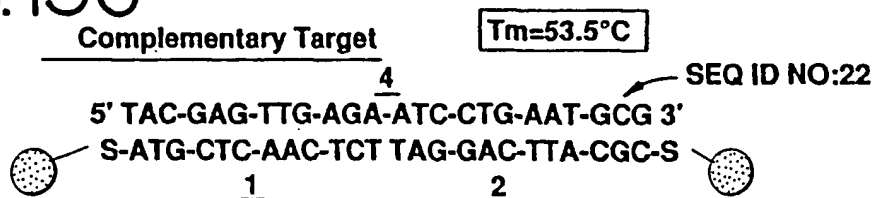


FIG. 15D

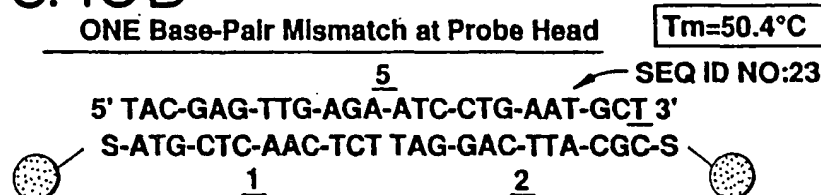


FIG. 15E

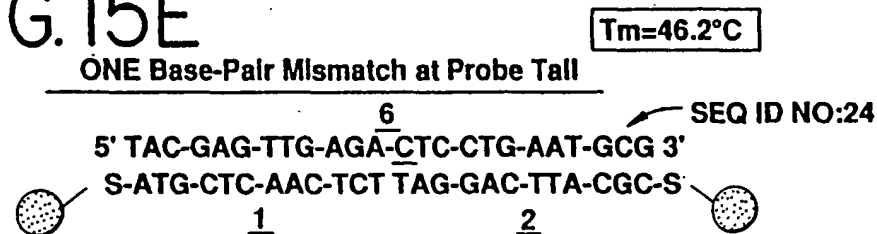


FIG. 15F

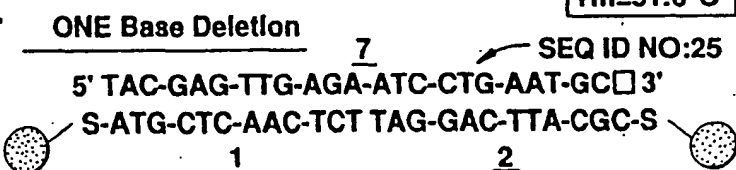
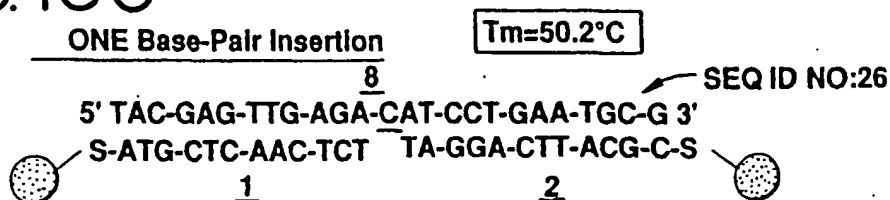


FIG. 15G



## FIG. 16A

24 Base Template

5' TAC-GAG-TTG-AGA-ATC-CTG-AAT-GCG 3'  
 —S-ATG-CTC-AAC-TCT TAG-GAC-TTA-CGC-S —  
 1 2

## FIG. 16B

48 Base Template with Complementary 24 Base Filler

5' TAC-GAG-TTG-AGA-CCG-TTA-AGA-CGA-GGC-AAT-CAT-GCA-ATC-CTG-AAT-GCG 3'  
 —S-ATG-CTC-AAC-TCT GGC-AAT-TCT-GCT-CCG-TTA-GTA-CGT TAG-GAC-TTA-CGC-S —  
 1 2

## FIG. 16C

72 Base Template with Complementary 48 Base Filler

5' TAC-GAG-TTG-AGA-CCG-TTA-AGA-CGA-GGC-AAT-CAT-GCA-TAT-ATT-GGA-CGC-TTT-ACG-GAC-AAC-ATC-CTG-AAT-GCG 3'  
 —S-ATG-CTC-AAC-TCT GGC-AAT-TCT-GCT-CCG-TTA-GTA-CGT-ATA-TAA-CCT-GCG-AAA-TGC-CTG-TTG TAG-GAC-TTA-CGC-S —  
 1 2

FIG. 17B

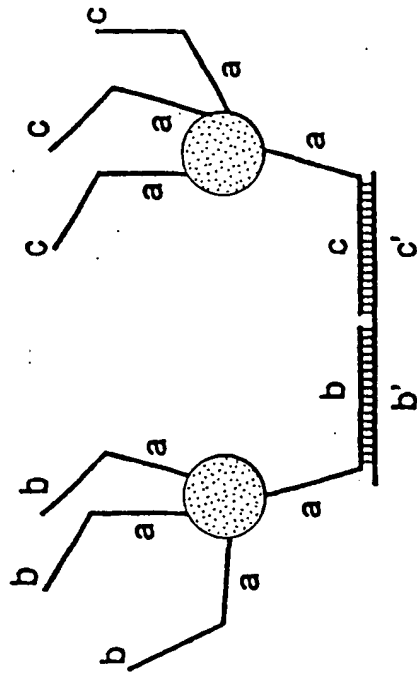


FIG. 17A

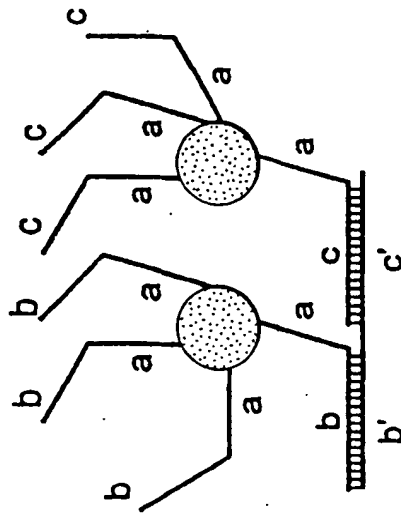


FIG. 17C

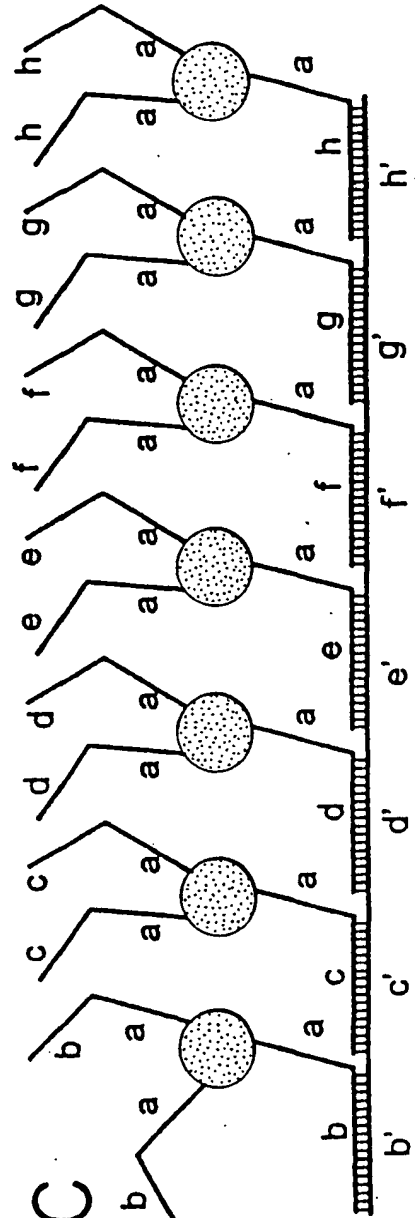


FIG. 17D

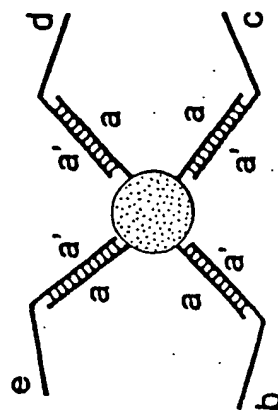
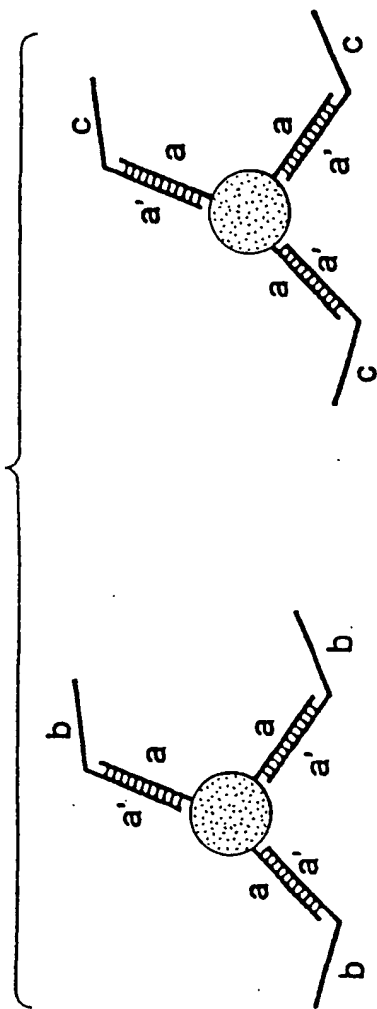


FIG. 17E

FIG. 18

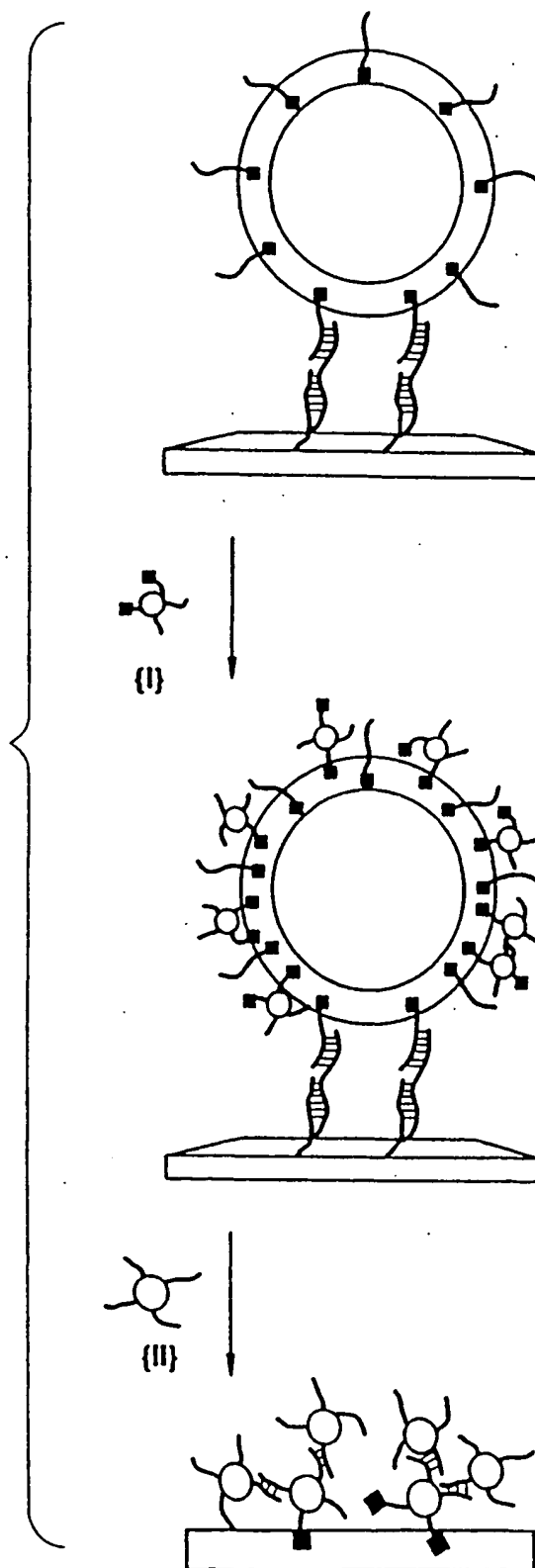


FIG. 19A

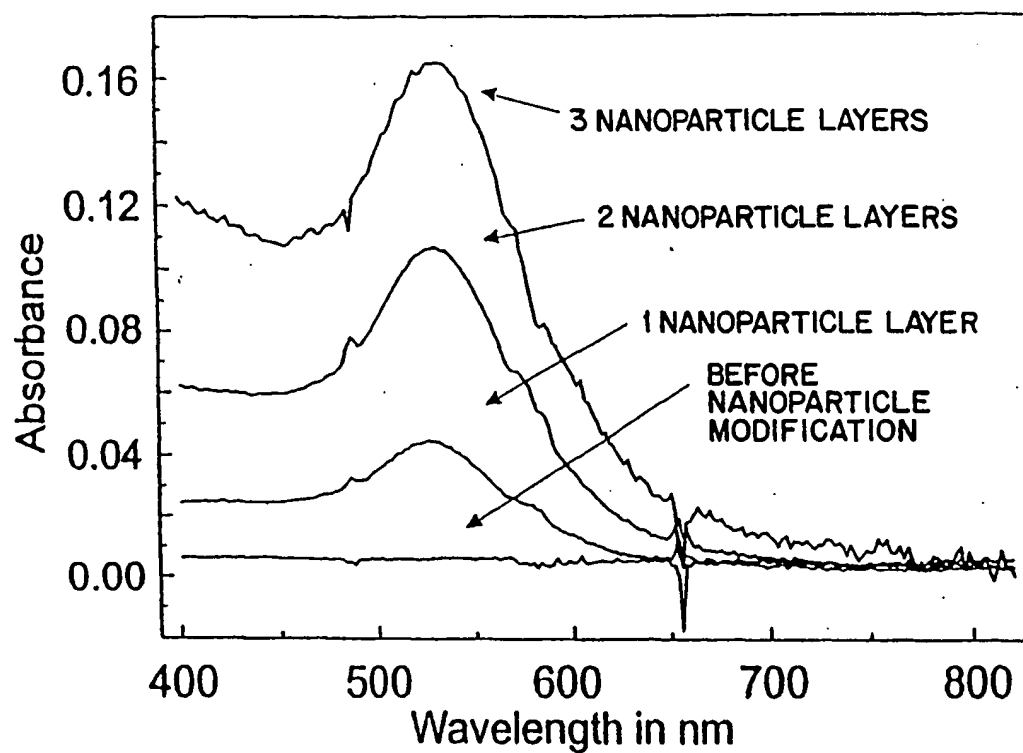


FIG. 19B

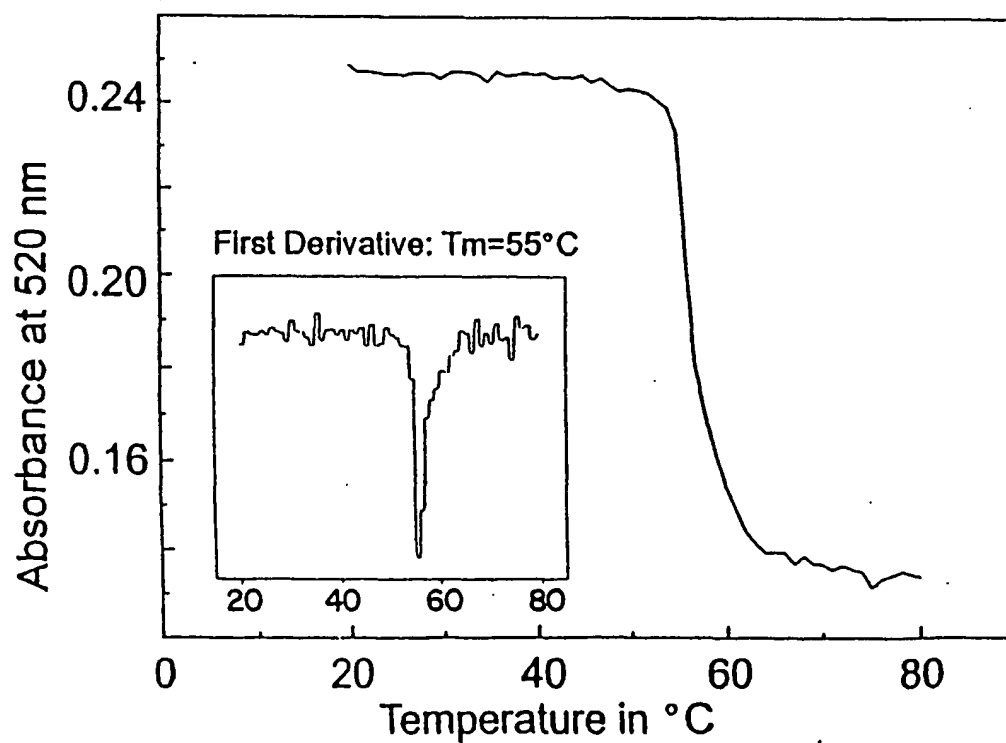


FIG. 20A

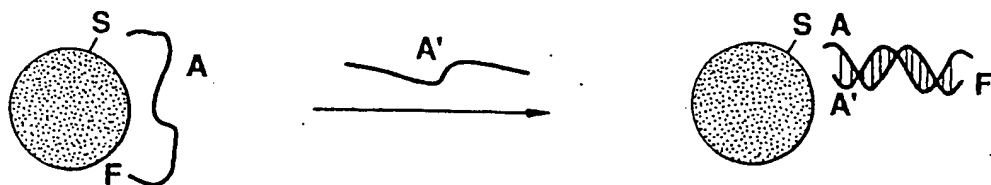
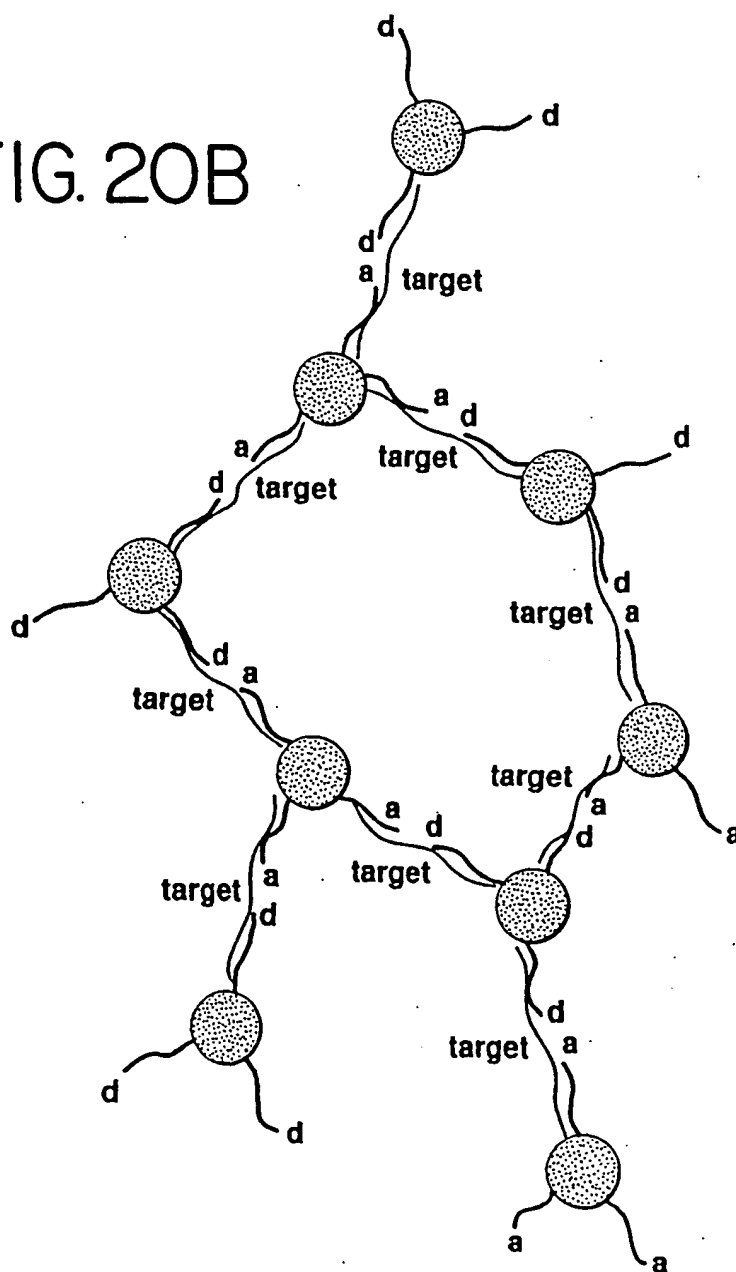


FIG. 20B



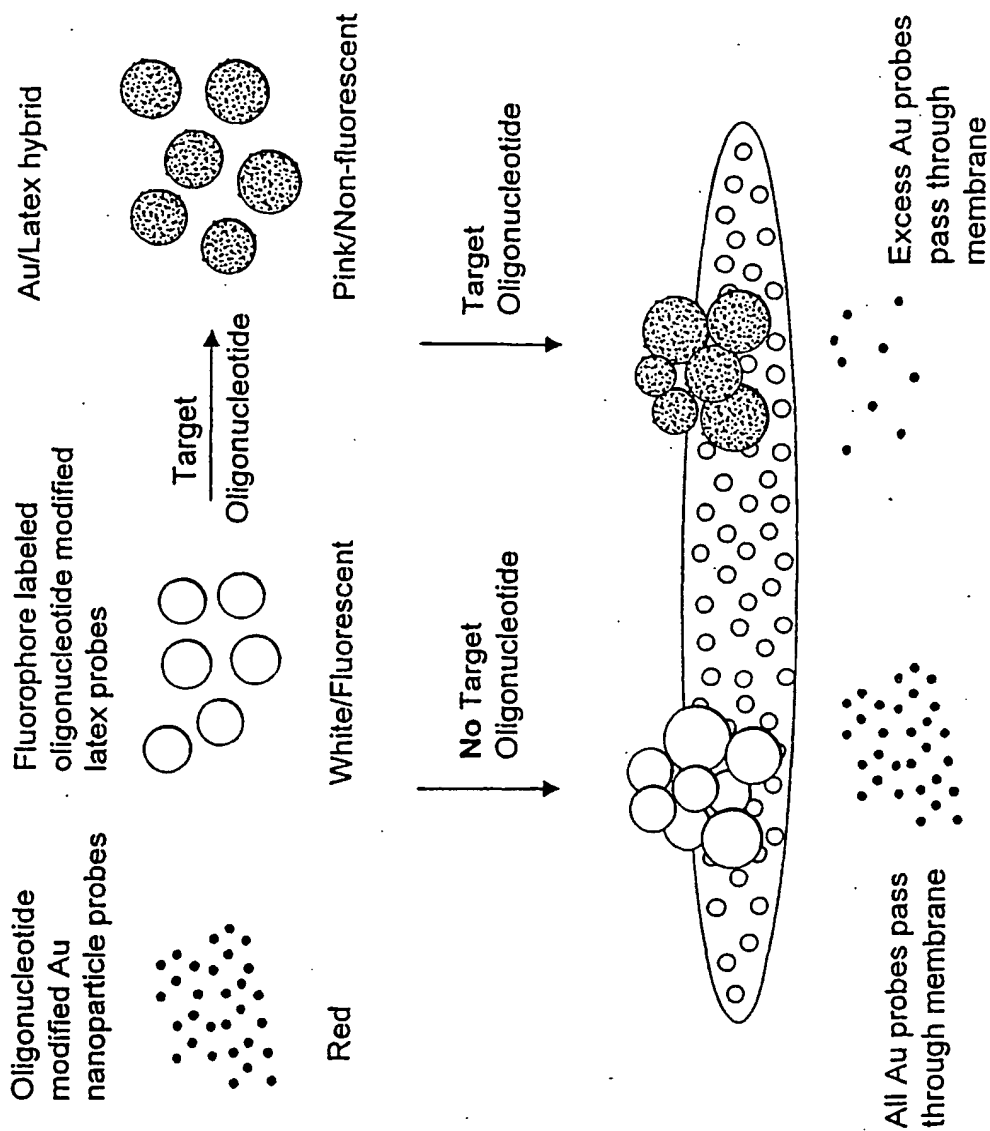
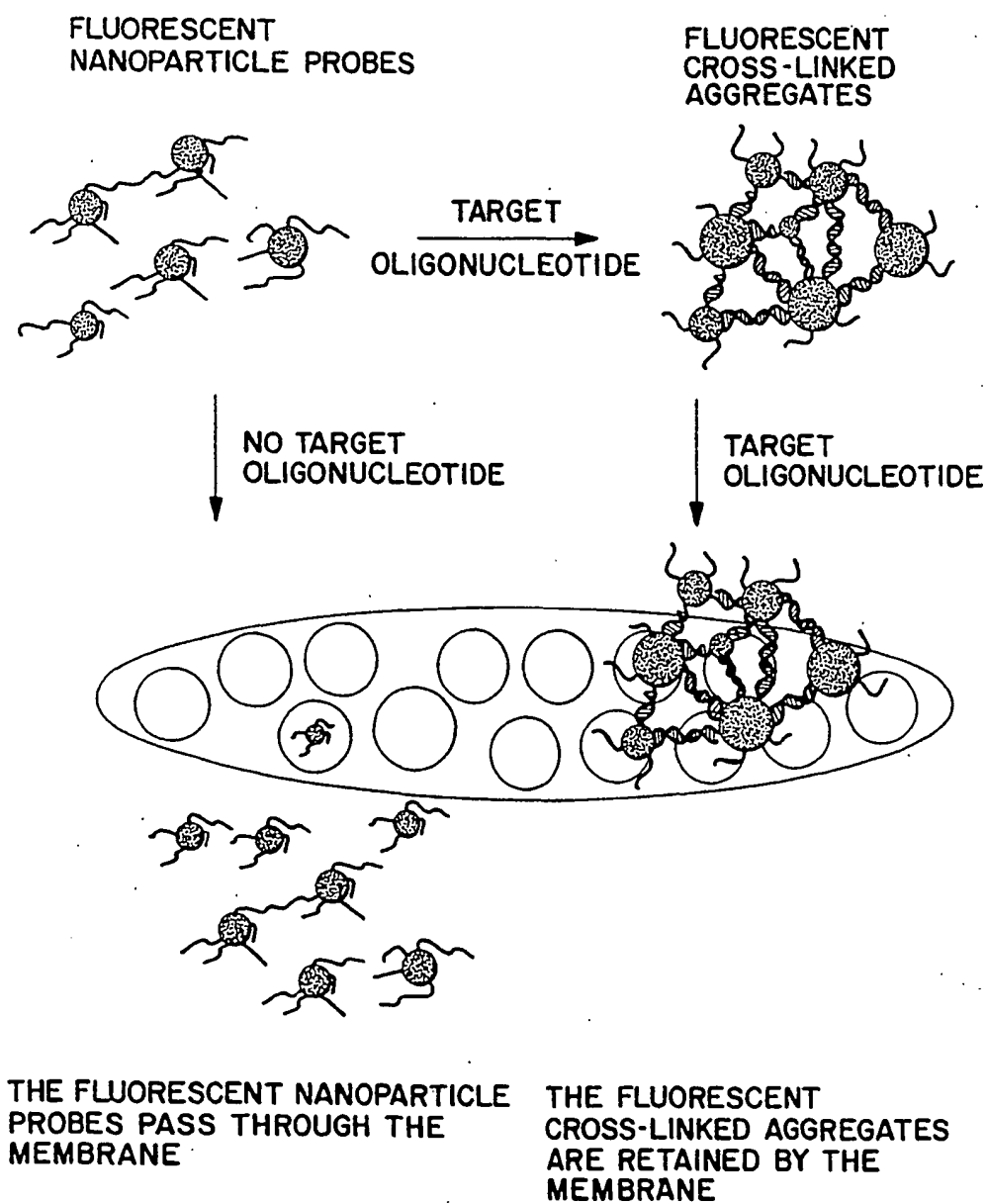


FIG. 22



# FIG. 23

## Anthrax PCR Product

5'G GCG GAT GAG TCA GTA GTT AAG GAG GCT CAT AGA GAA GTA ATT AAT  
3'C CGC CTA CTC AGT CAT CAA TTC CTC CGA GTA TCT CTT CAT TAA TTA

TCG TCA ACA GAG GGA TTA TTG TTA AAT ATT GAT AAG GAT ATA AGA AAA  
AGC AGT TGT CTC CCT AAT AAC AAT TTA TAA CTA TTC CTA TAT TCT TTT

ATA TTA TCC AGG GTT ATA TTG TAG AAA TTG AAG ATA CTG AAG GGC TT 3'  
TAT AAT AGG TCC CAA TAT AAC ATC TTT AAC TTC TAT GAC TTC CCG AA 5'

**141 mer Anthrax PCR product** [SEQ ID NO:36]

3' CTC CCT AAT AAC AAT — 

[SEQ ID NO:37]

3' TTA TAA CTA TTC CTA — 

[SEQ ID NO:38]

Oligonucleotide-Nanoparticle Probes

## Blocker Oligonucleotides

3' C CGC CTA CTC AGT CAT CAA TTC CTC CGA GT  
3' A TCT CTT CAT TAA TTA AGC AGT TGT  
3' TAT TCT TTT TAT AAT AGG TCC CAA TAT  
3' AAC ATC TTT AAC TTC TAT GAC TTC CCG AA

[SEQ ID NO:39]  
[SEQ ID NO:40]  
[SEQ ID NO:41]  
[SEQ ID NO:42]

FIG. 24

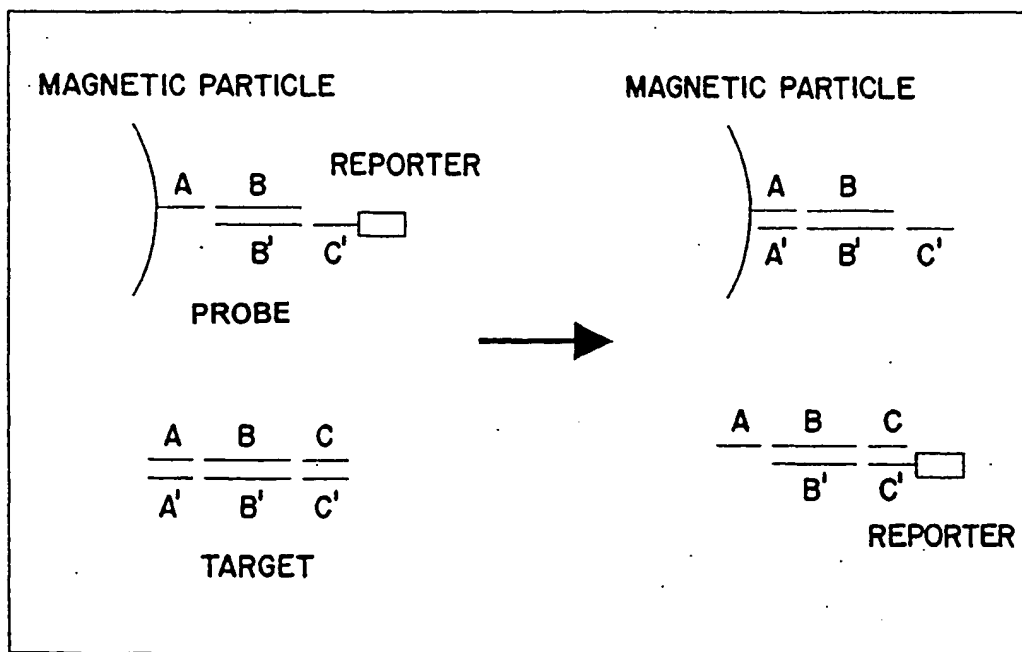
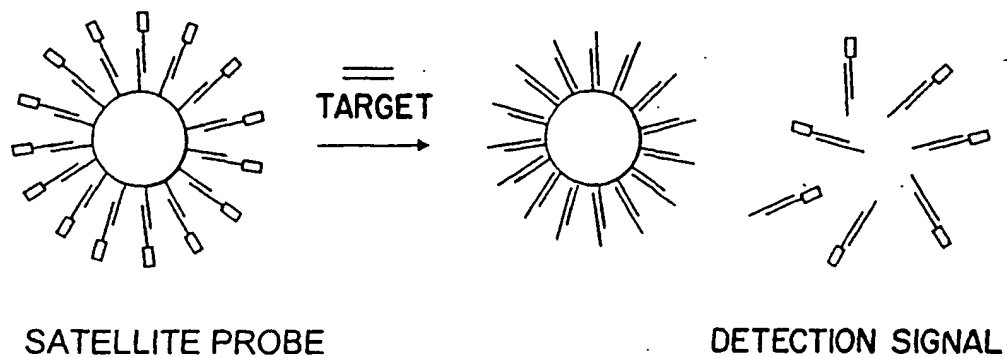




FIG. 26A

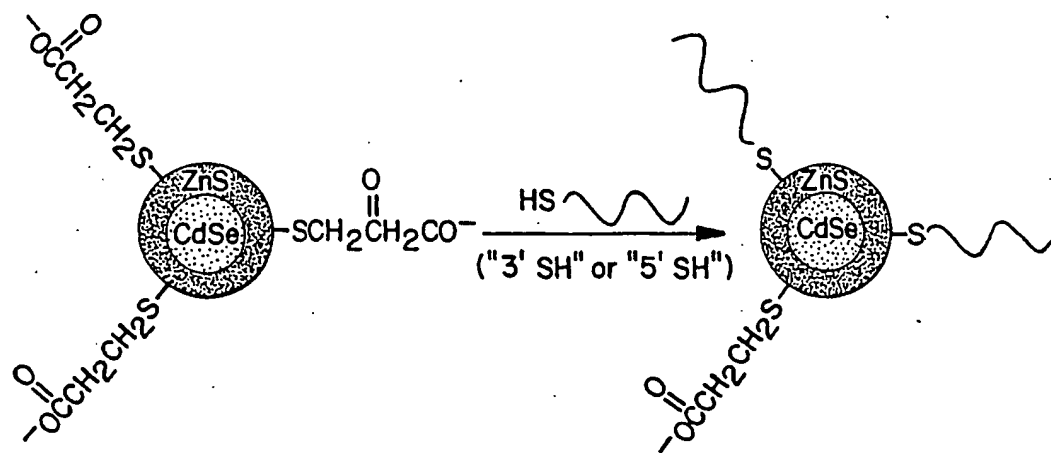


FIG. 26B

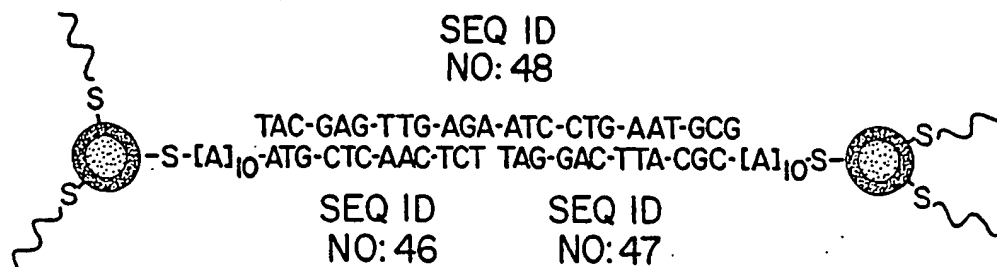


FIG. 27A

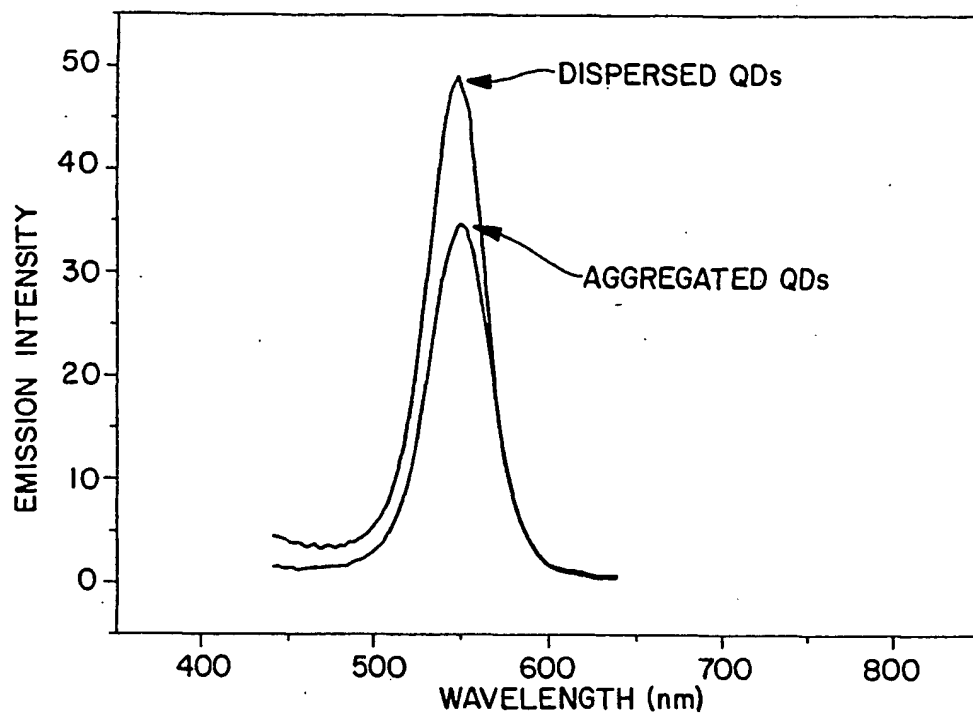


FIG. 27B

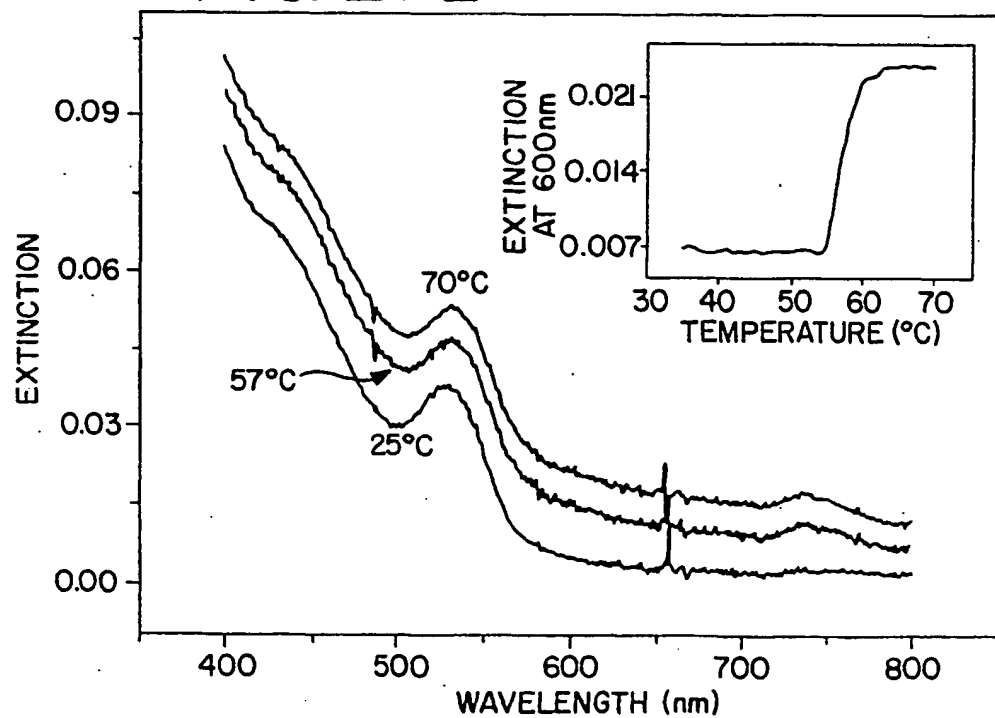


FIG. 27C

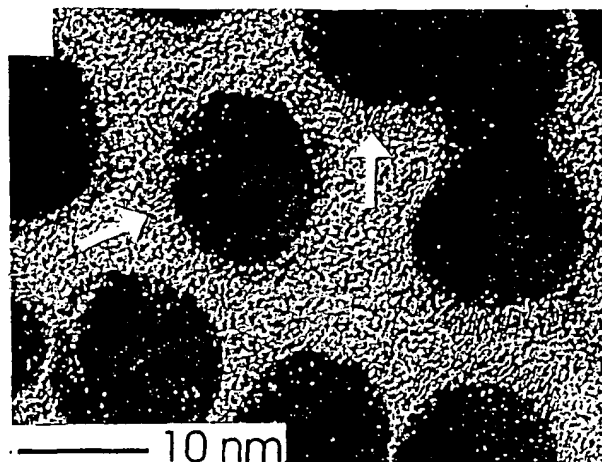


FIG. 27D

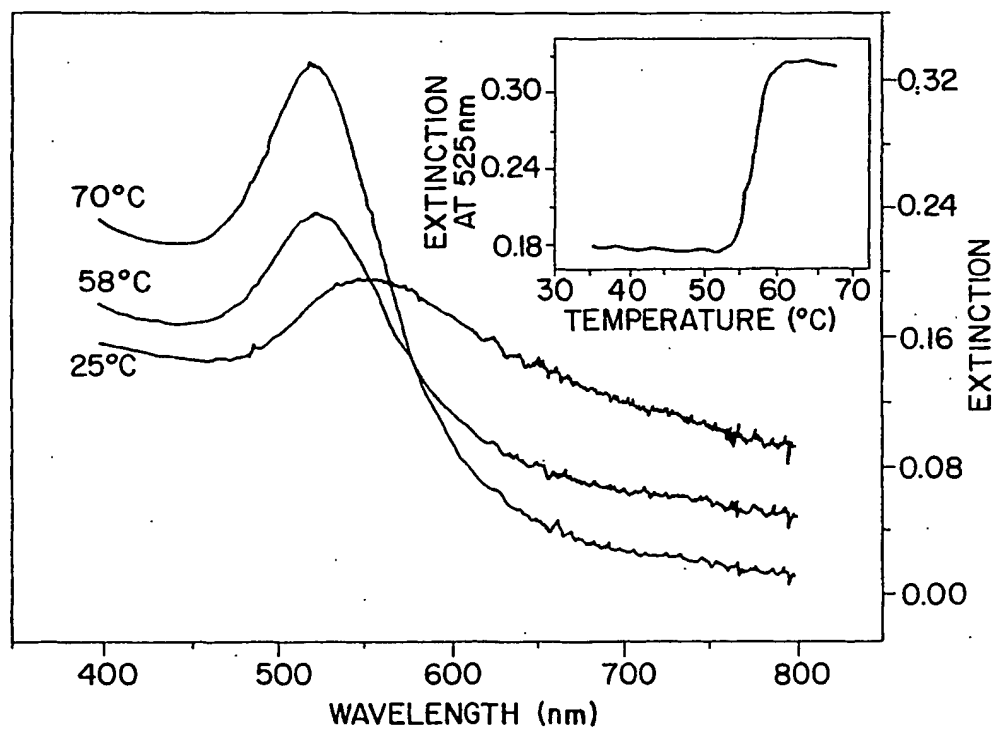


FIG. 28A

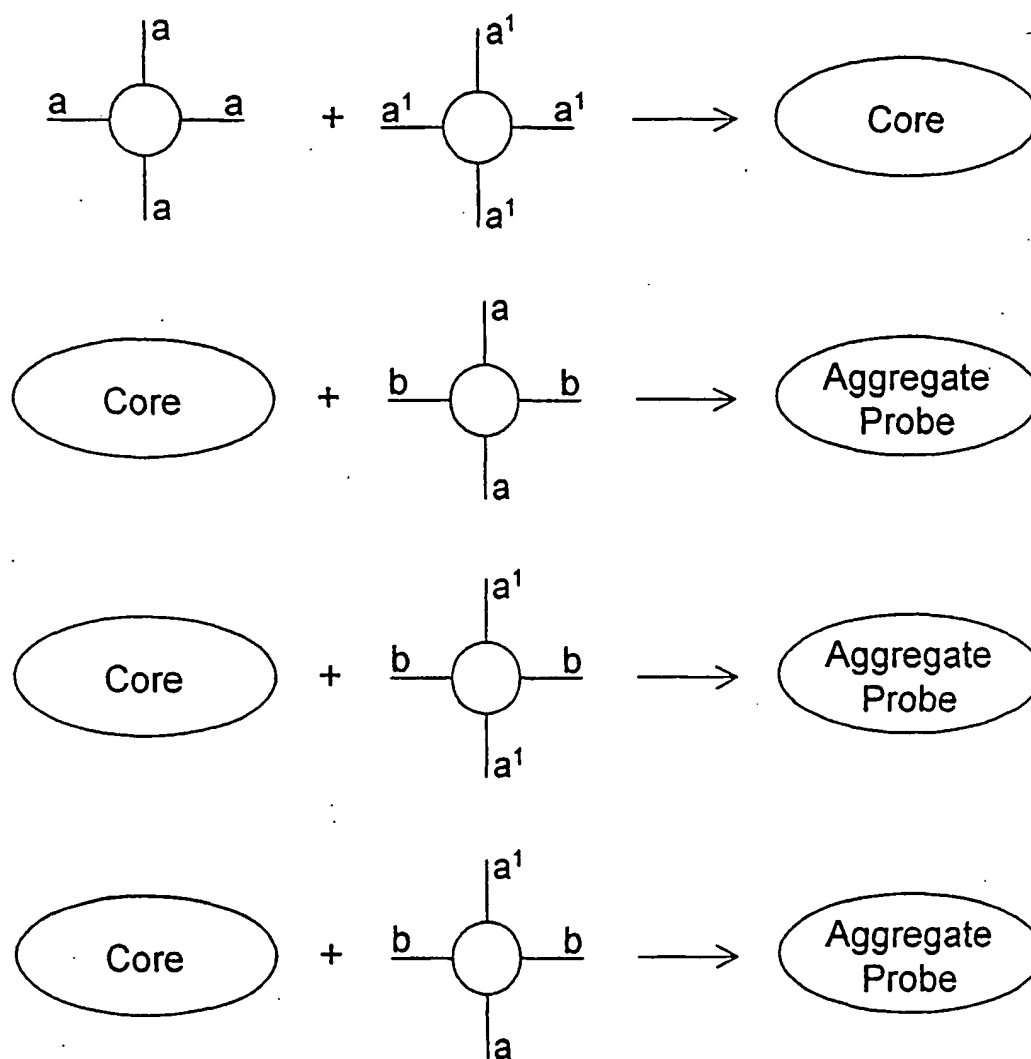


FIG. 28B

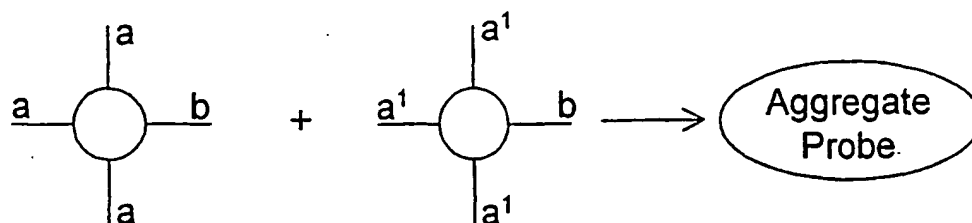


FIG. 28C

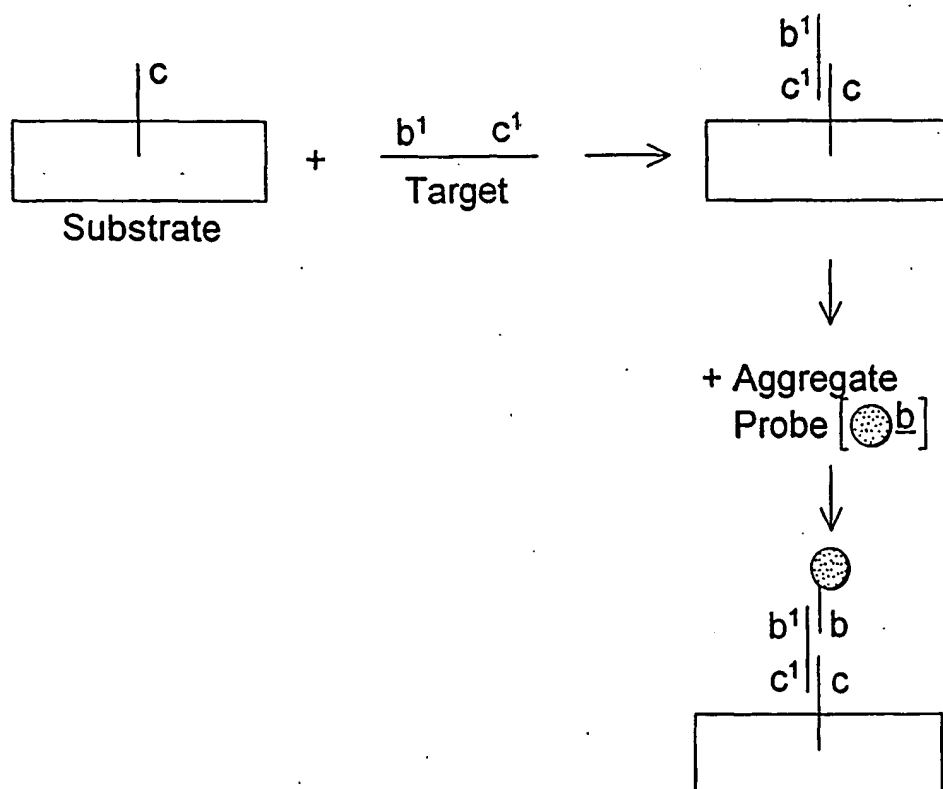


FIG. 28D

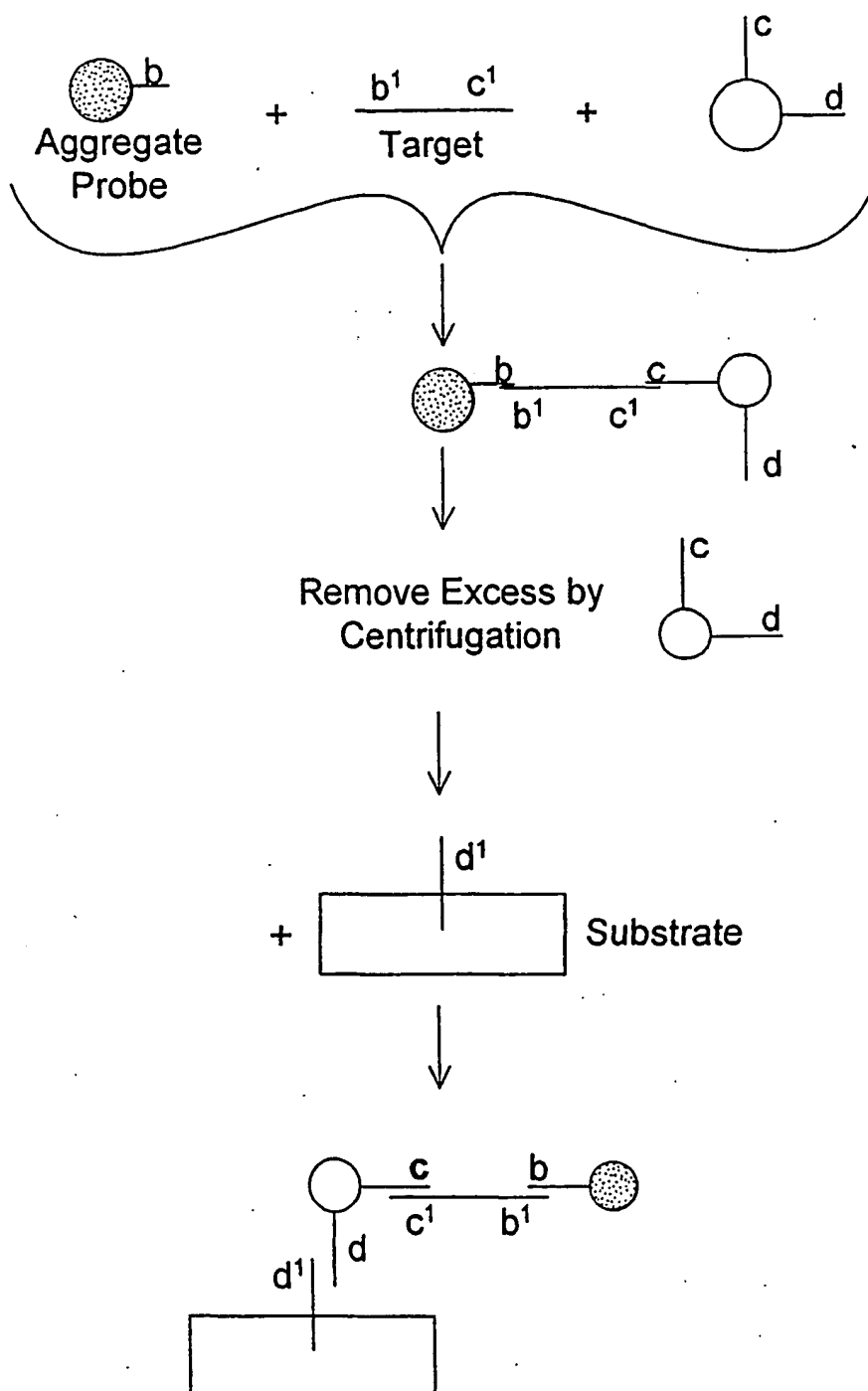
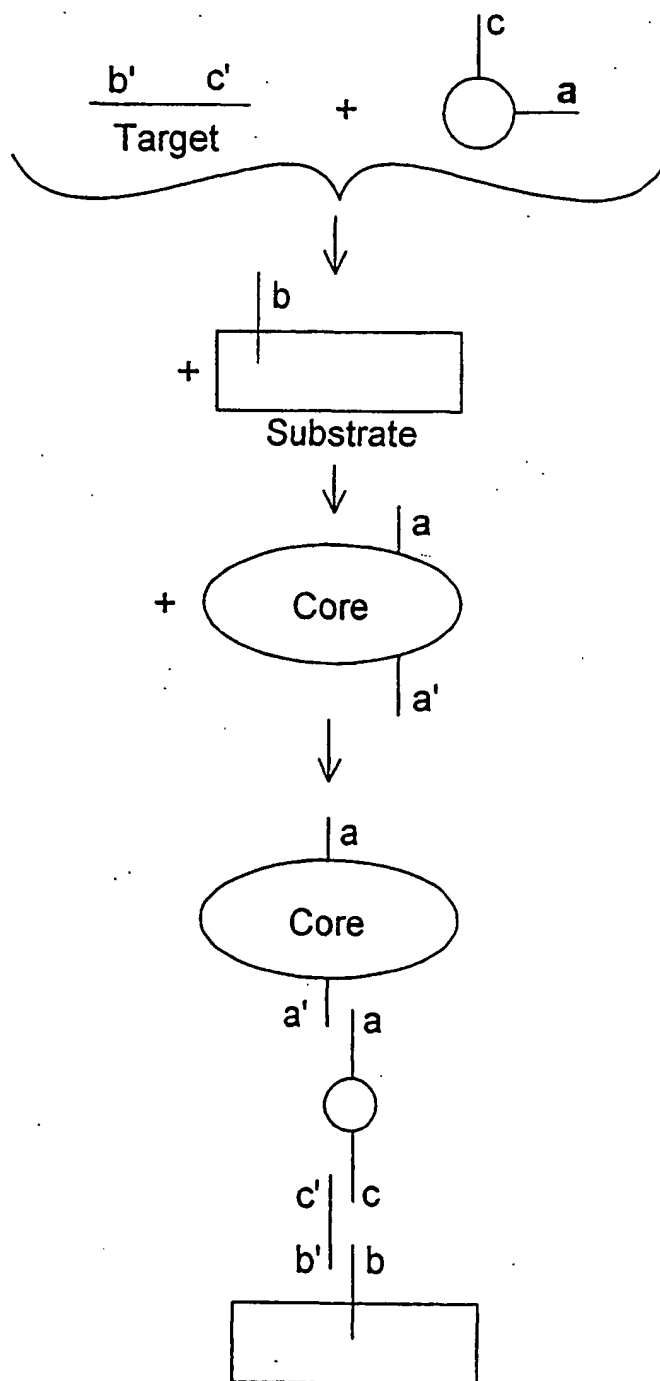


FIG. 28E



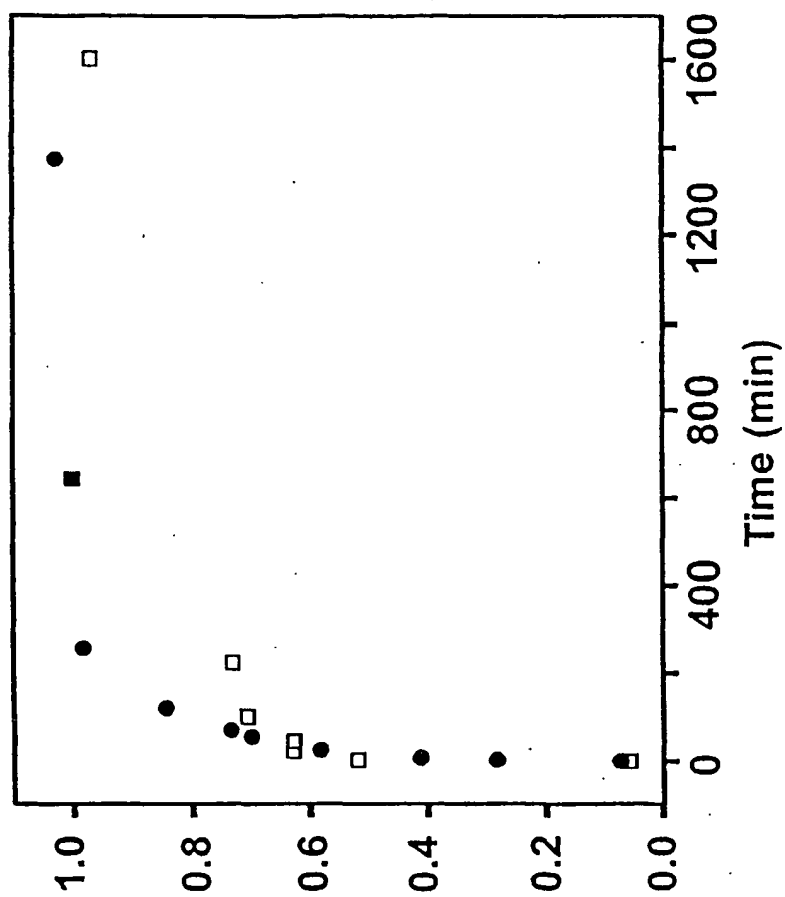


FIG. 29

Fractional Displacement by ME

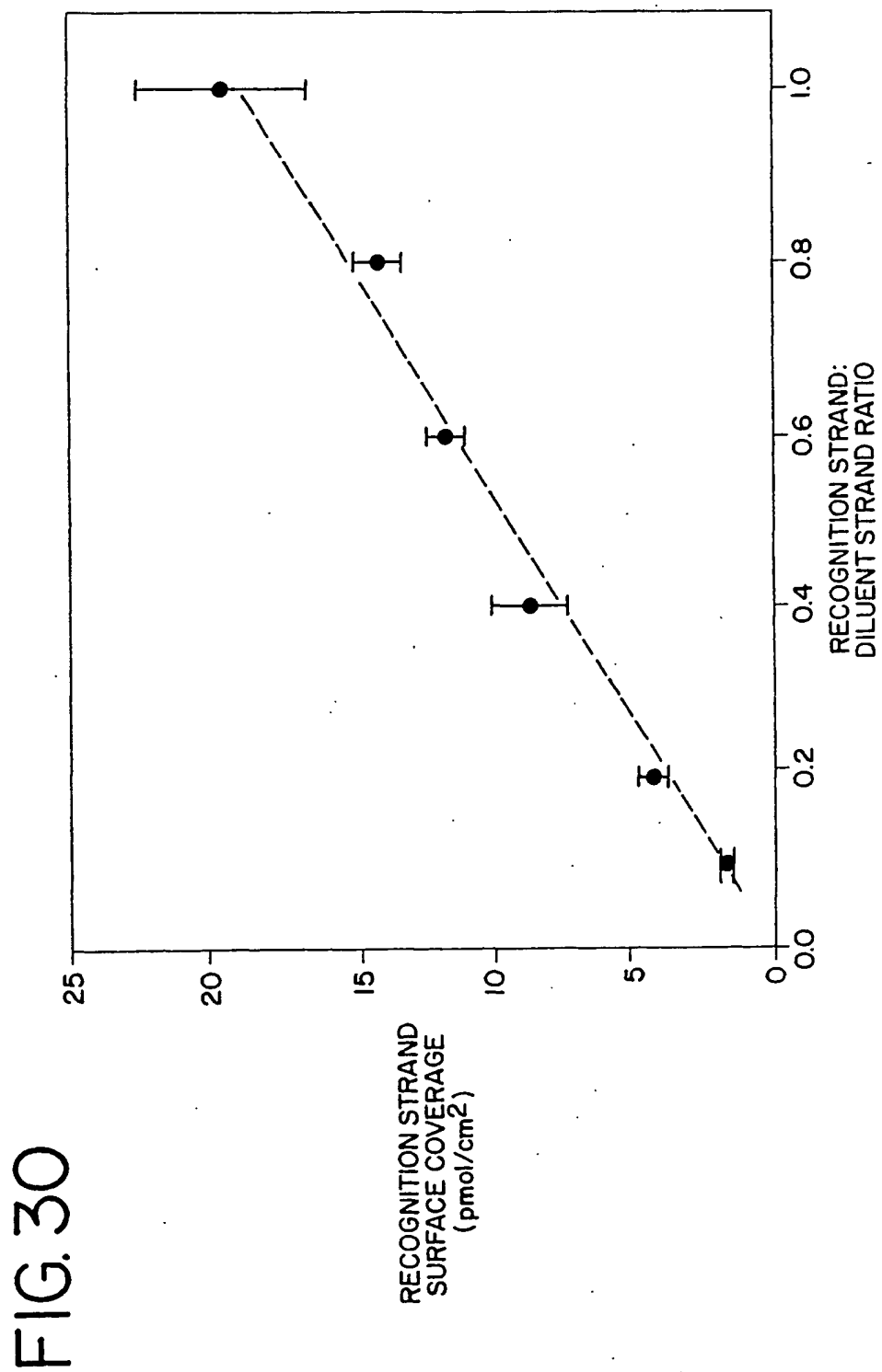
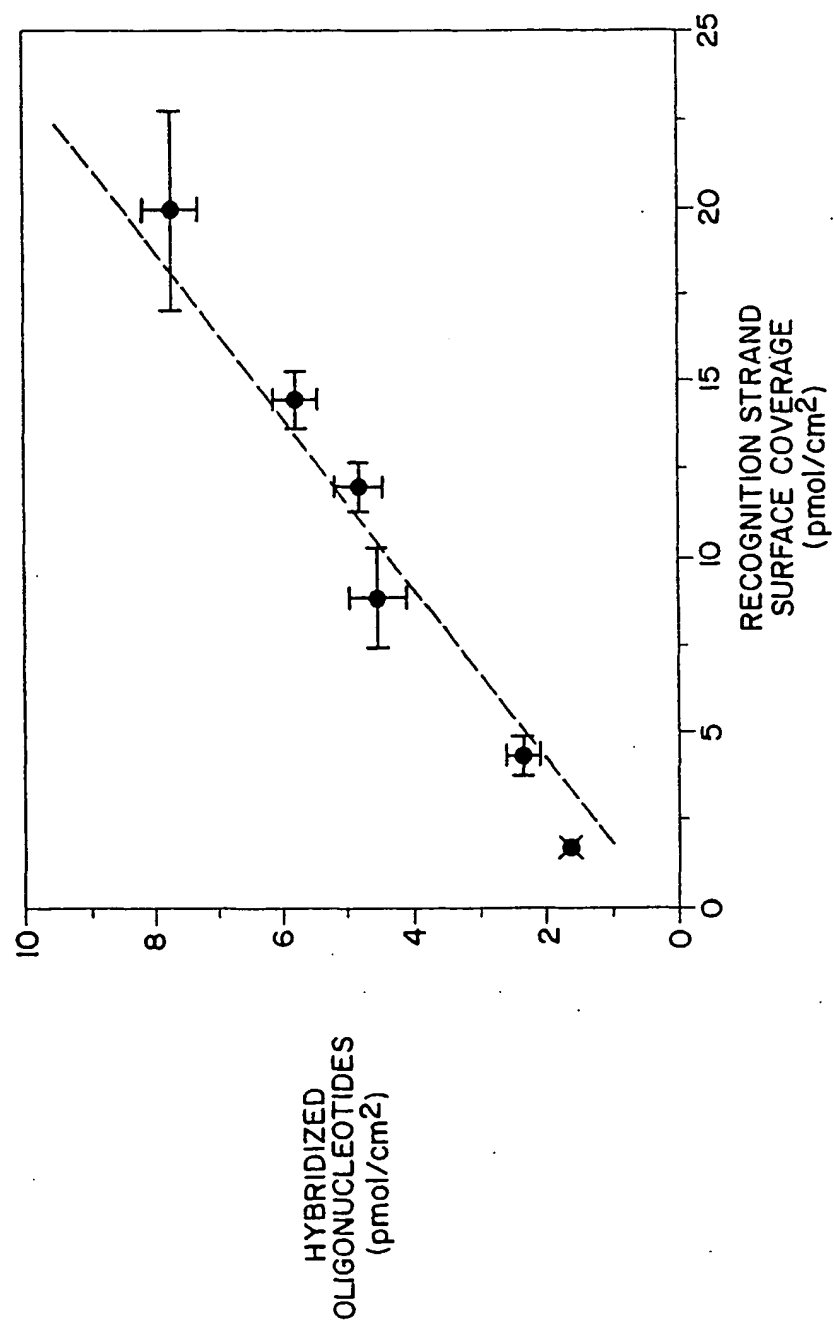
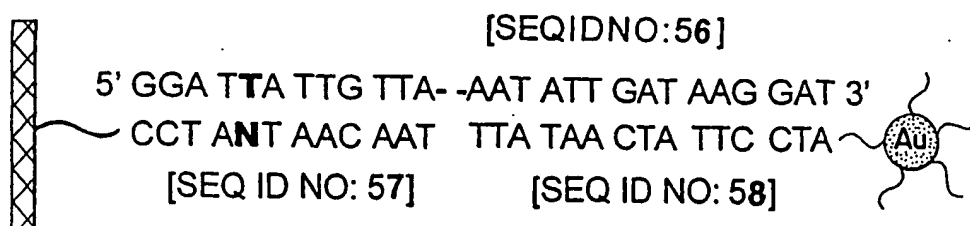


FIG. 31



## FIG. 32



**N** = A (complementary),  
G,C,T (mismatched)

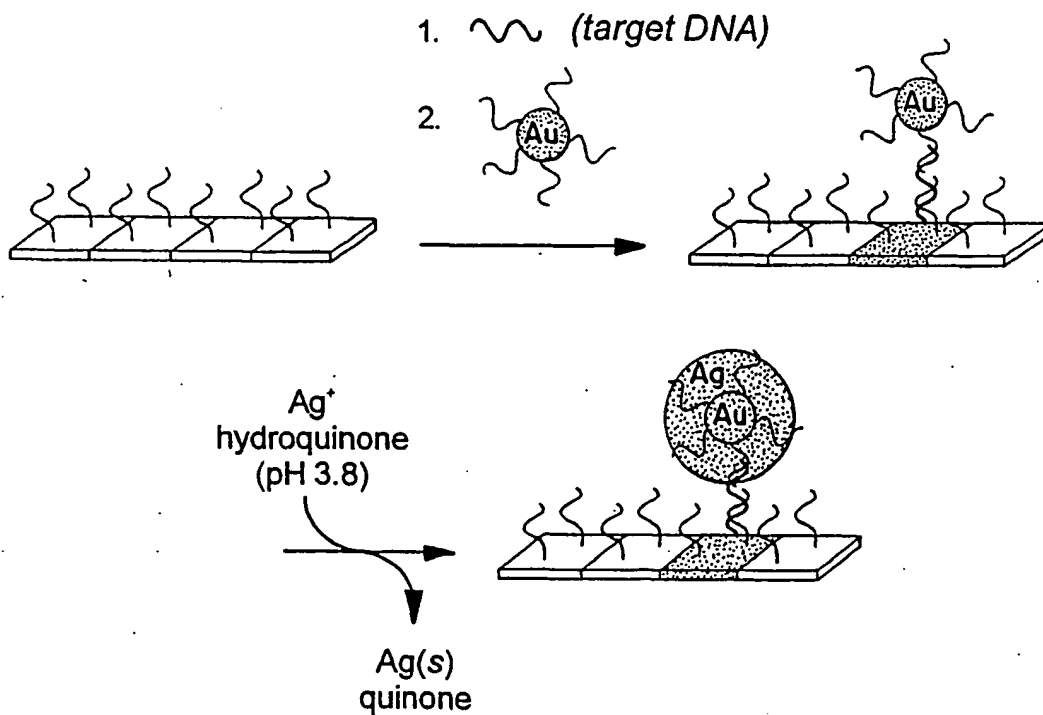


FIG. 33

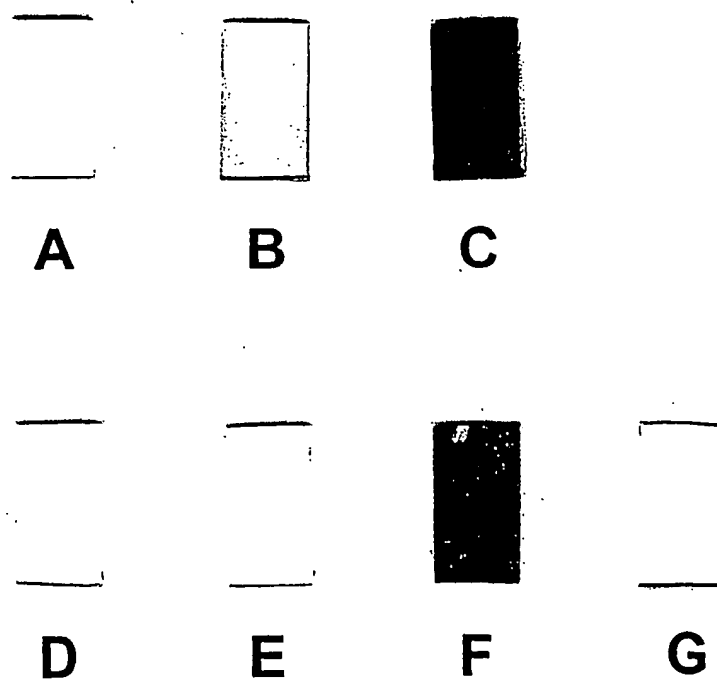


FIG. 34

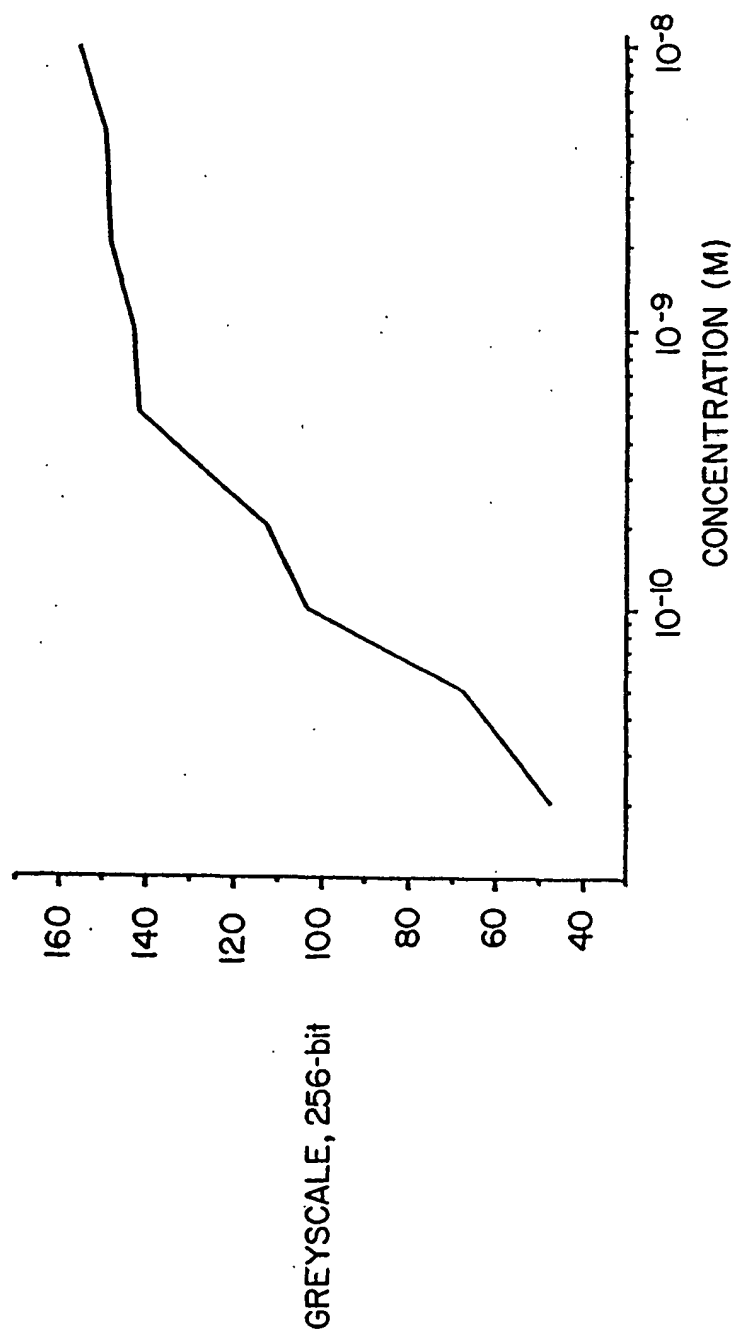


FIG.35A

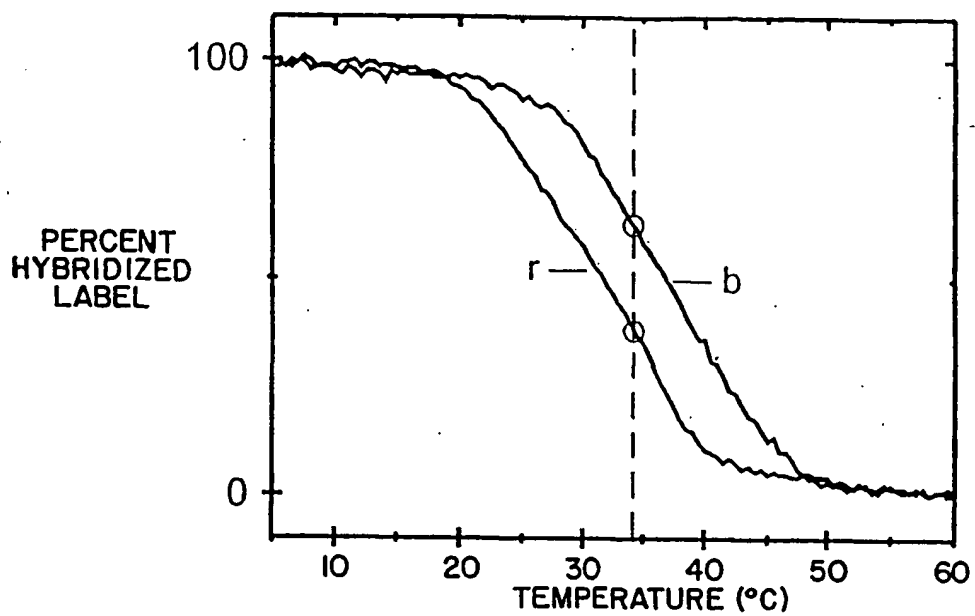


FIG.35B

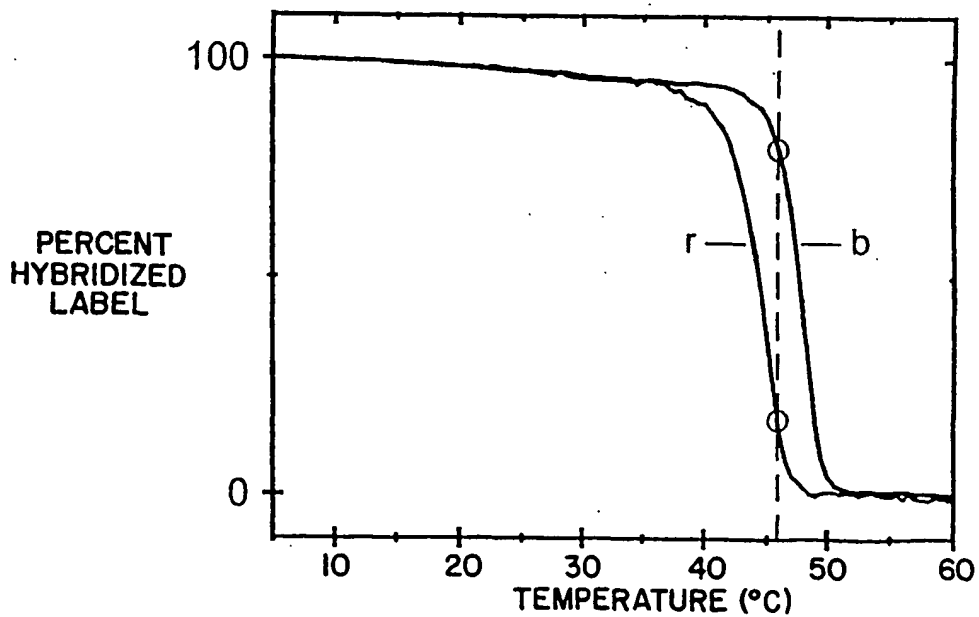


FIG. 36A

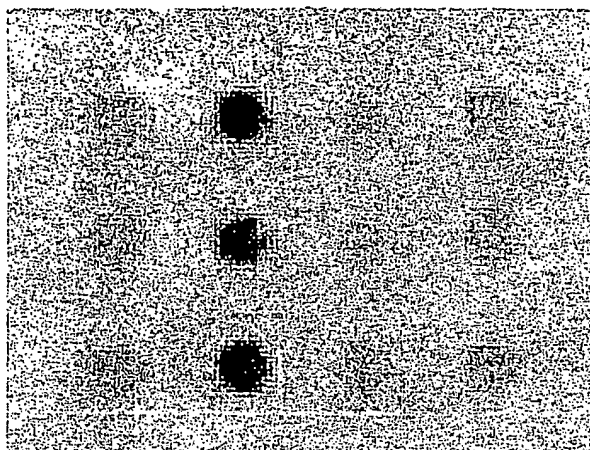
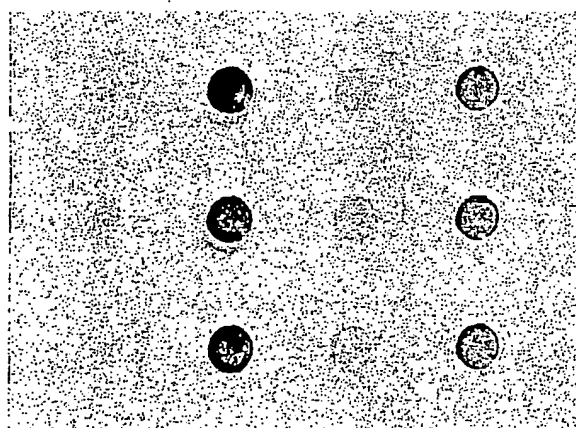


FIG. 36B



C A T G

FIG.37A

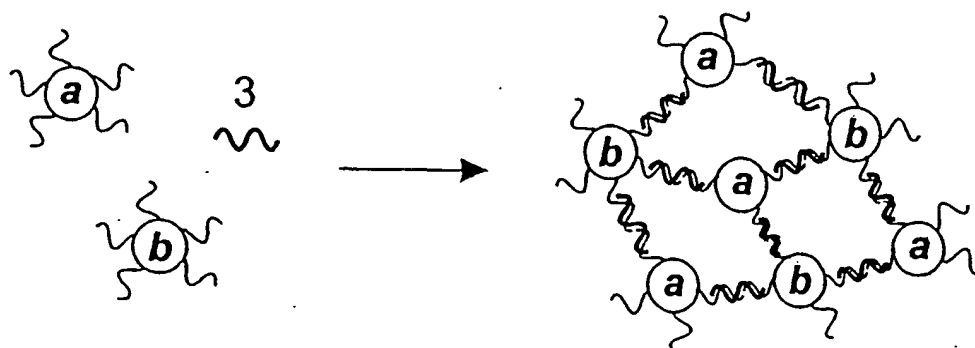


FIG.37B

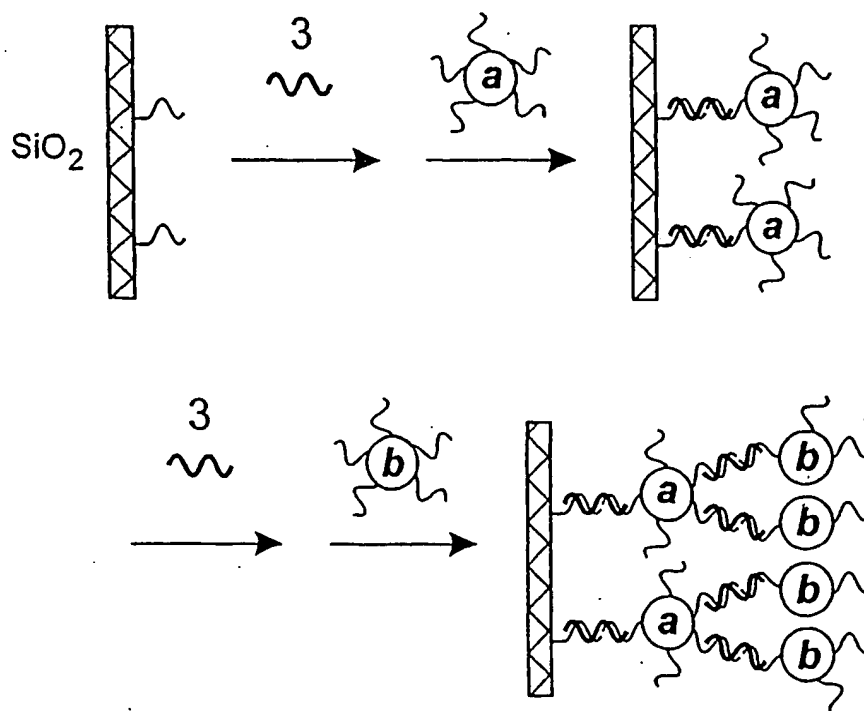


FIG. 38A

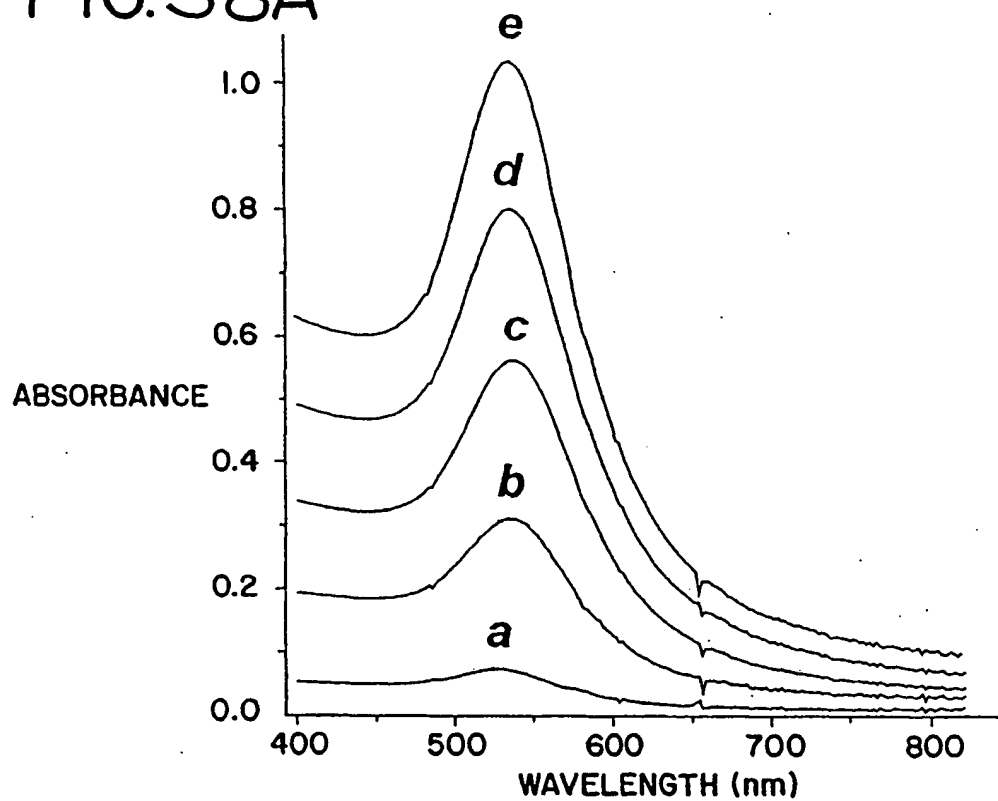


FIG. 38B

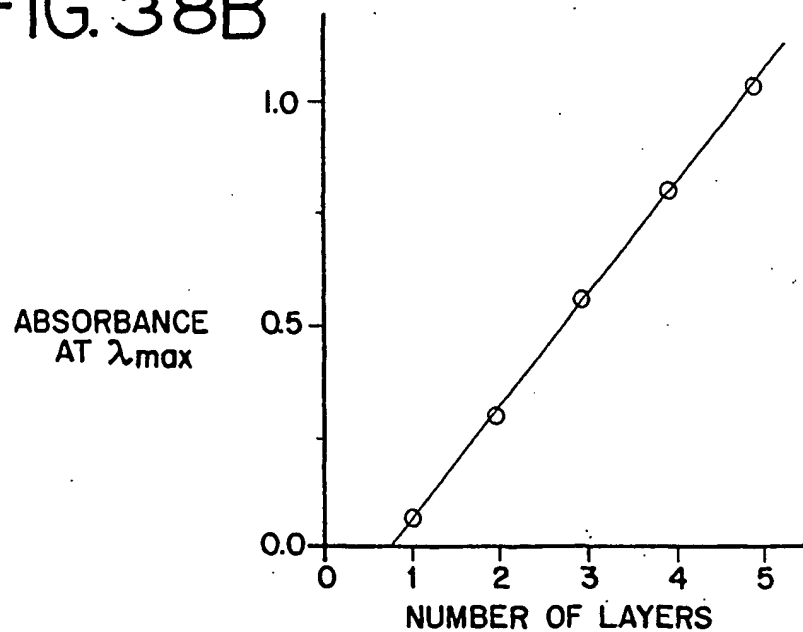


FIG. 39A

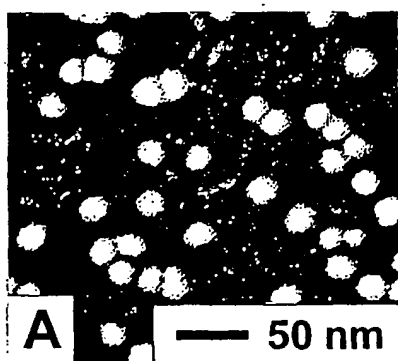


FIG. 39B

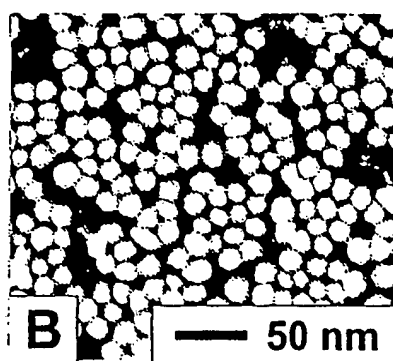


FIG.39C

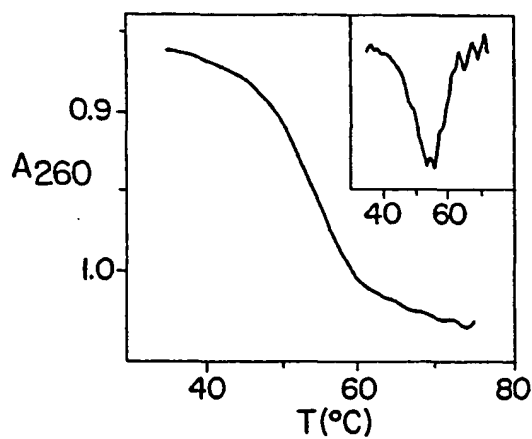


FIG.39D

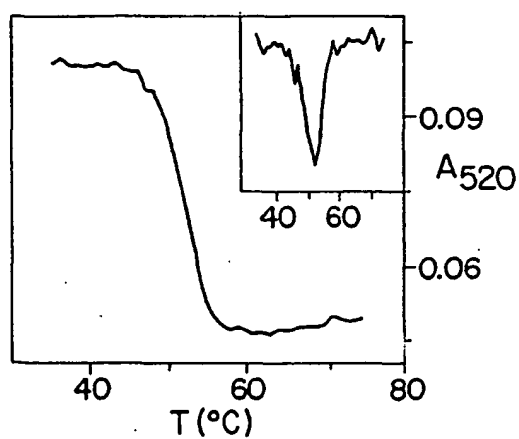


FIG.39E

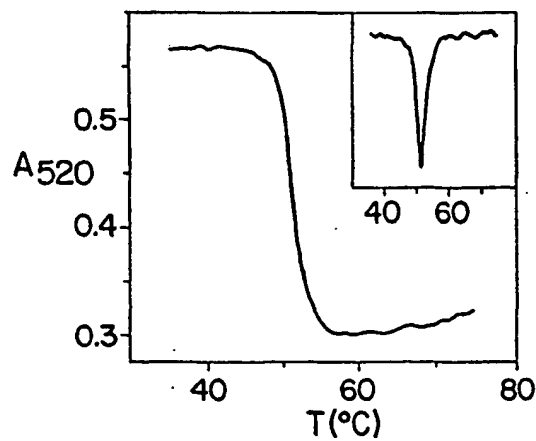


FIG.39F

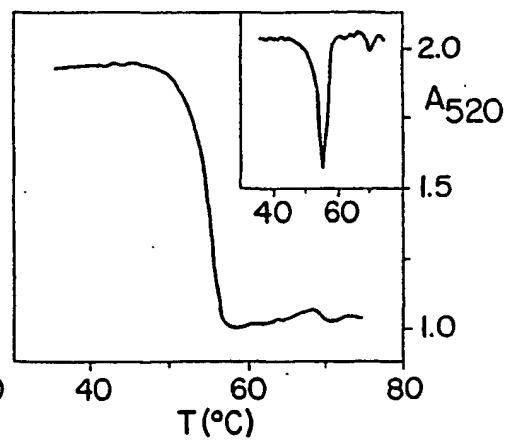


FIG. 40

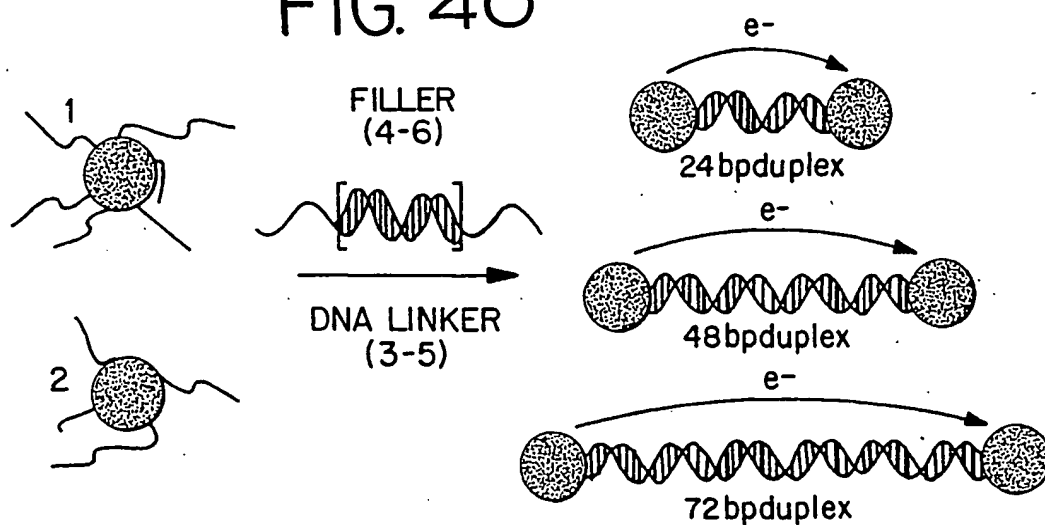
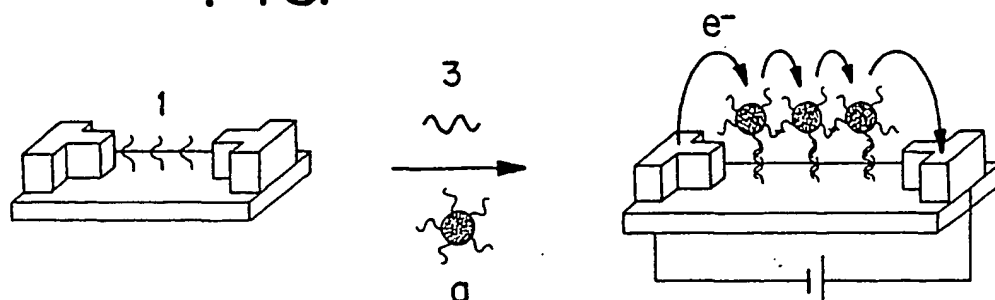
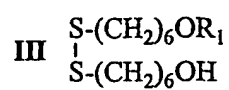
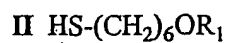
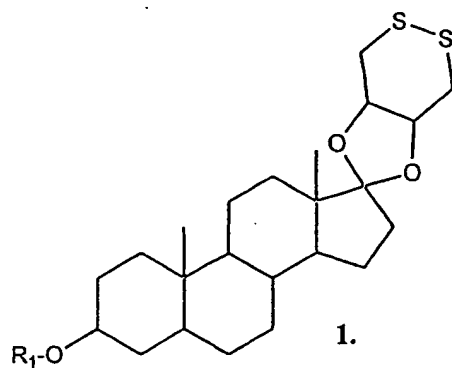


FIG. 41



## FIG. 42



R<sub>1</sub>

a = H

b = (iPr)<sub>2</sub>NP(OCH<sub>2</sub>CH<sub>2</sub>CN)-

c1 = 5'-p(A<sub>20</sub>)-TATCGTTCCATCAGCT [SEQ ID NO: 65]

c2 = 5'-p(A<sub>20</sub>)-TTGATCTTCCGTTCT [SEQ ID NO: 66]

Target I = 79-mer oligonucleotide with target region:

3'-.....ATAGCAAGGTAGTCGAGCAACTAGAAAGGCAAGA.....5'  
[SEQ ID NO: 67]

FIG. 43

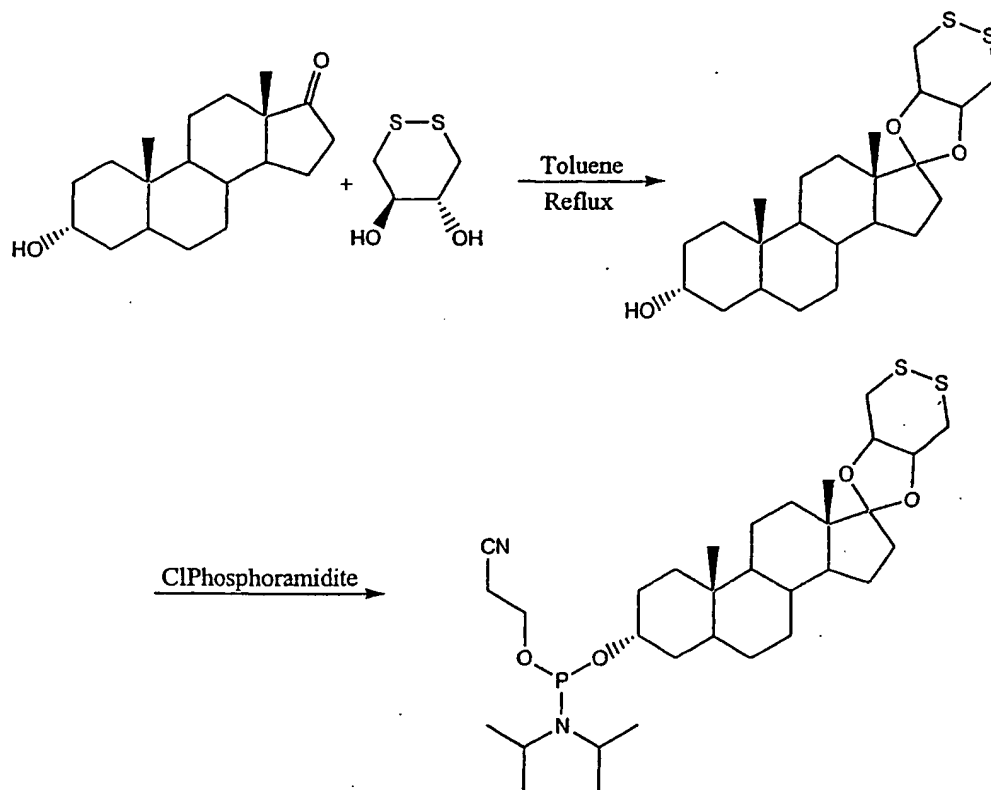
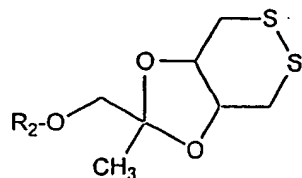


FIG. 44



2.

 $R_2$ 

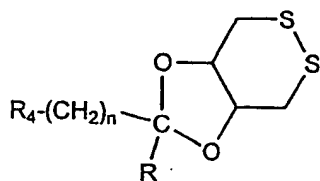
a = H

b = (iPr)<sub>2</sub>NP(OCH<sub>2</sub>CH<sub>2</sub>CN)-c1 = 5'-p(A<sub>20</sub>)-GCAGACCTCA [SEQ ID NO: 68]c2 = 5'-p(A<sub>20</sub>)-CCTATGTGTCG [SEQ ID NO: 69]D = 5'-p(A<sub>20</sub>) [SEQ ID NO: 70]

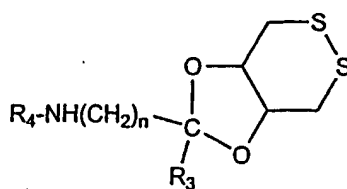
Target I = 63-mer oligonucleotide with target region:

3'-.....CGTCTGGAGTGGATACACAGC.....5'

[SEQ ID NO: 71]



3.



4.

 $R_3$  = hydrogen, an alkyl group, an aryl group, or a substituted alkyl or aryl group $R_4$  = an attached oligonucleotide or modified oligonucleotide

FIG. 45

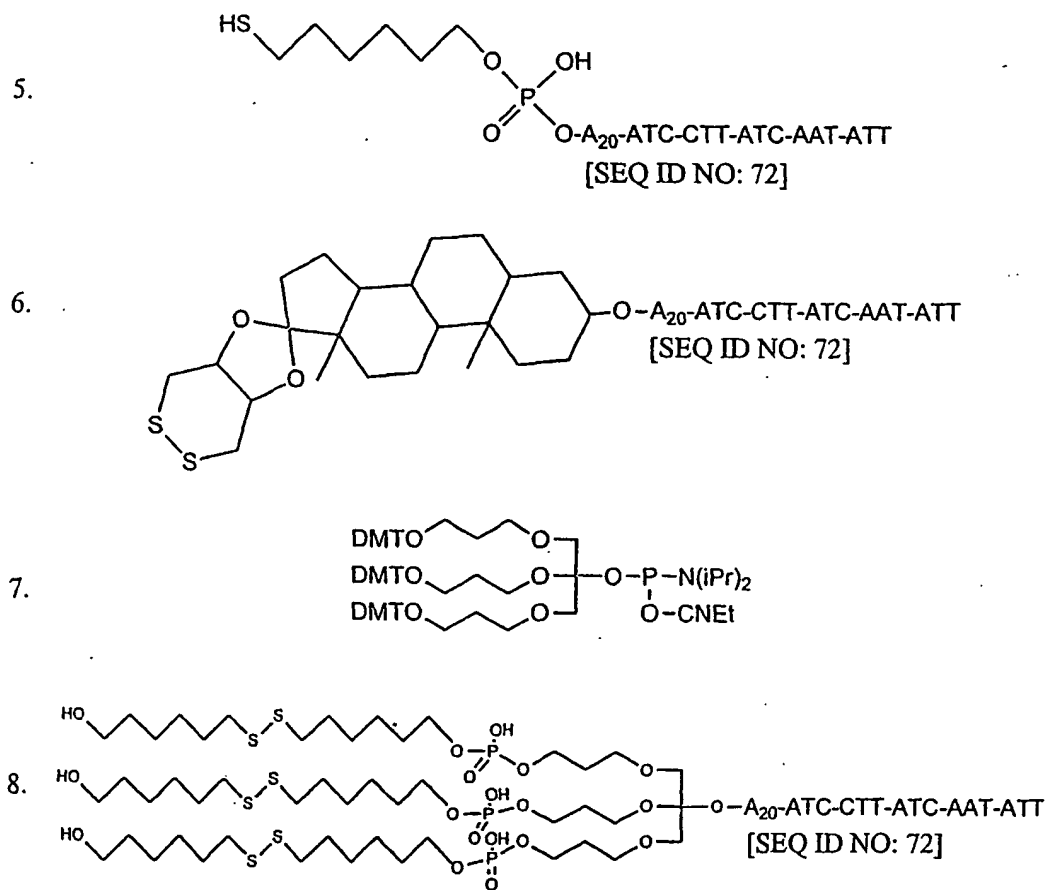
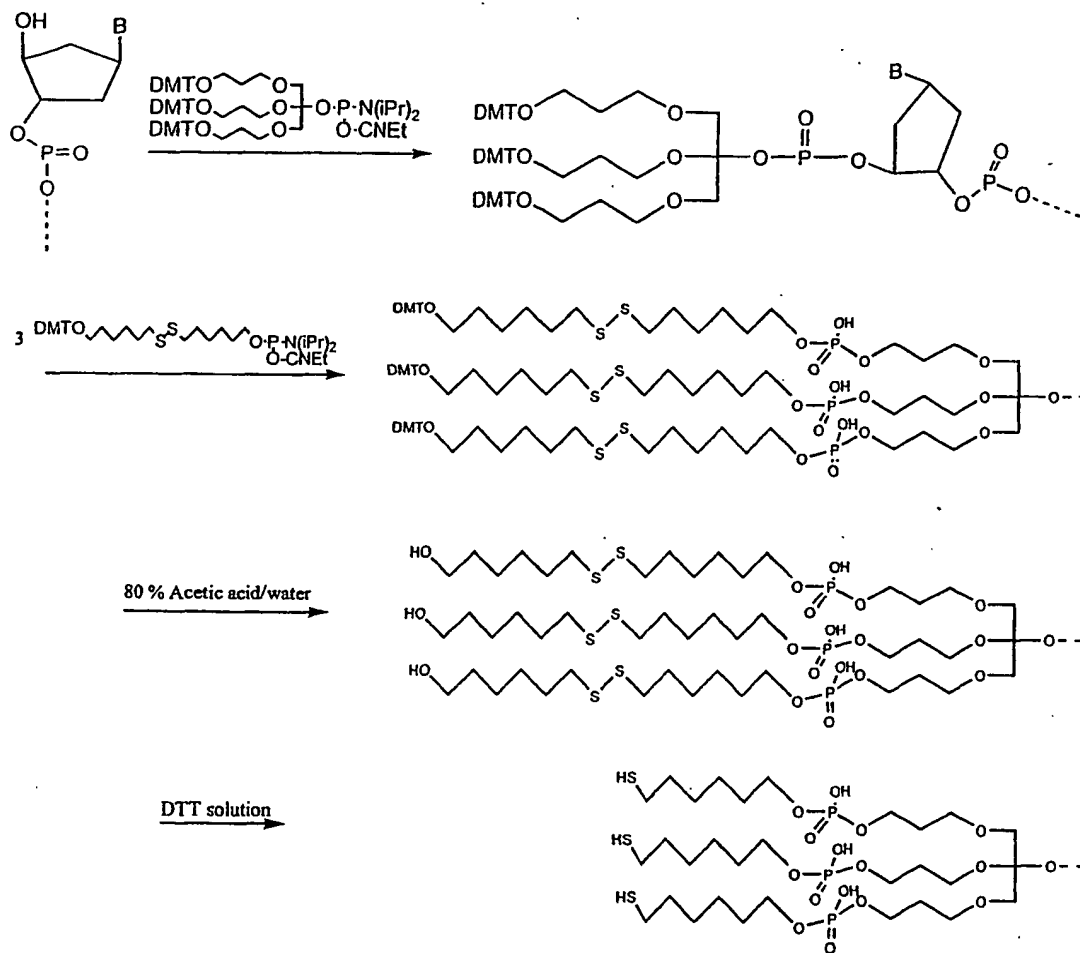


FIG. 46



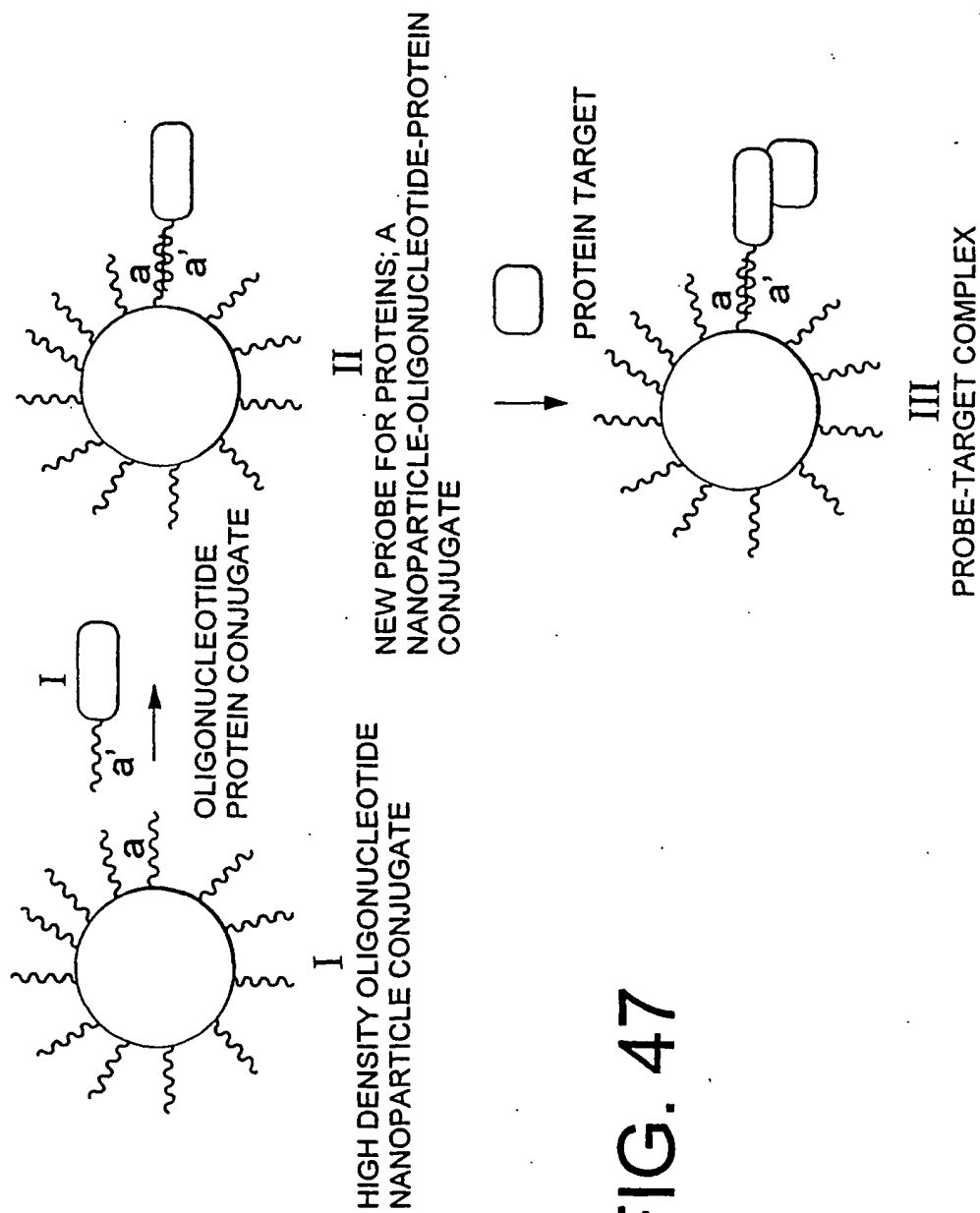
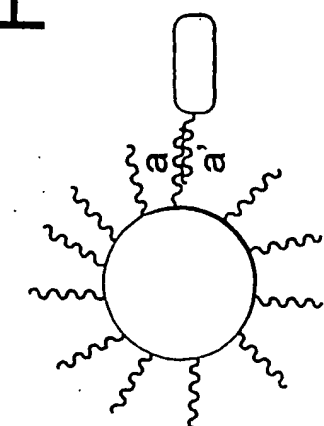


FIG. 47

FIG. 48

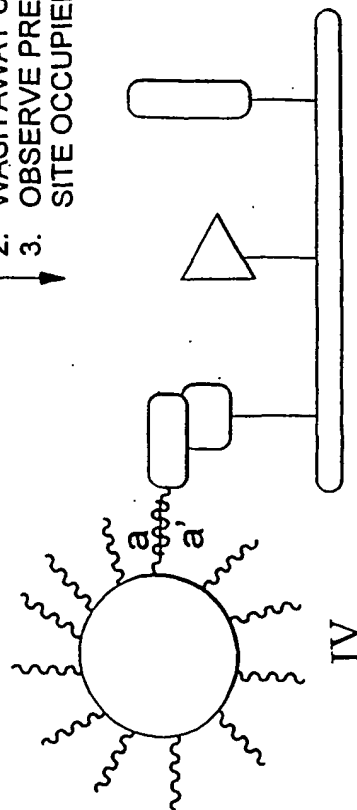


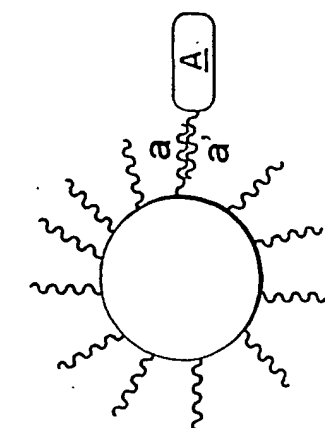
GLASS PLATE WITH THREE DIFFERENT PROTEINS IMMOBILIZED ON THE SURFACE, ONE OF WHICH BINDS TO THE PROTEIN IN PROBE II

II

NEW PROBE FOR PROTEINS; A NANOPARTICLE-OLIGONUCLEOTIDE-PROTEIN CONJUGATE

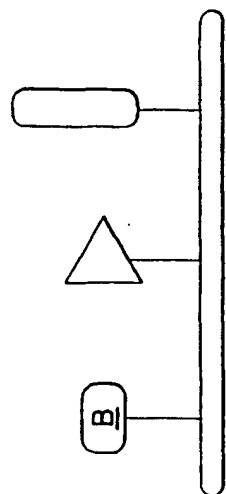
1. EXPOSE PLATE TO THE PROBE SOLUTION
2. WASH AWAY UNBOUND NANOPARTICLE PROBE
3. OBSERVE PRESENCE OF BOUND NANOPARTICLES AT SITE OCCUPIED BY THE FIRST PROTEIN IN THE SERIES.





II'

NANOPARTICLE-OLIGONUCLEOTIDE-RECEPTOR



GLASS PLATE WITH THREE DIFFERENT SUBSTANCES  
IMMOBILIZED ON THE SURFACE, ONE OF WHICH (B)  
BINDS TO THE RECEPTOR UNIT (A) IN II'.

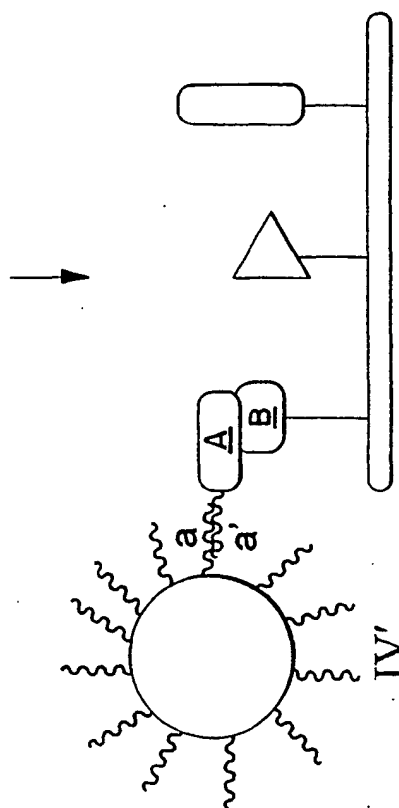


FIG. 49

FIG. 51A

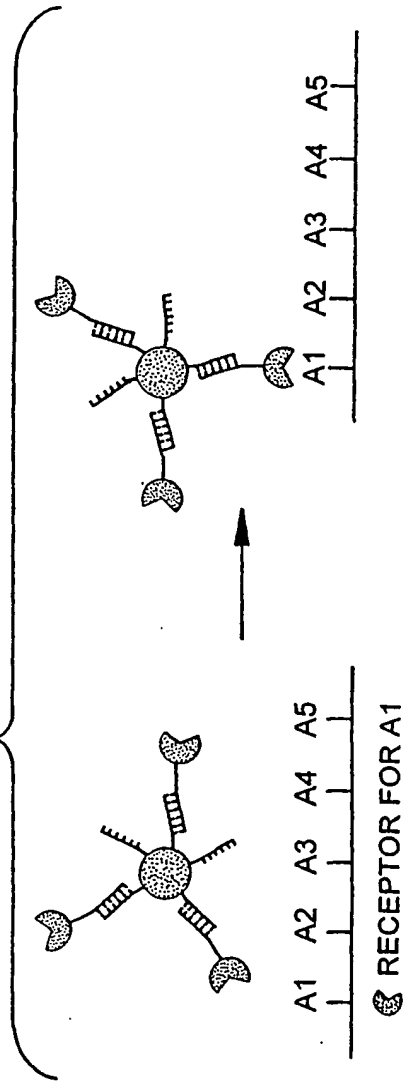


FIG. 51B

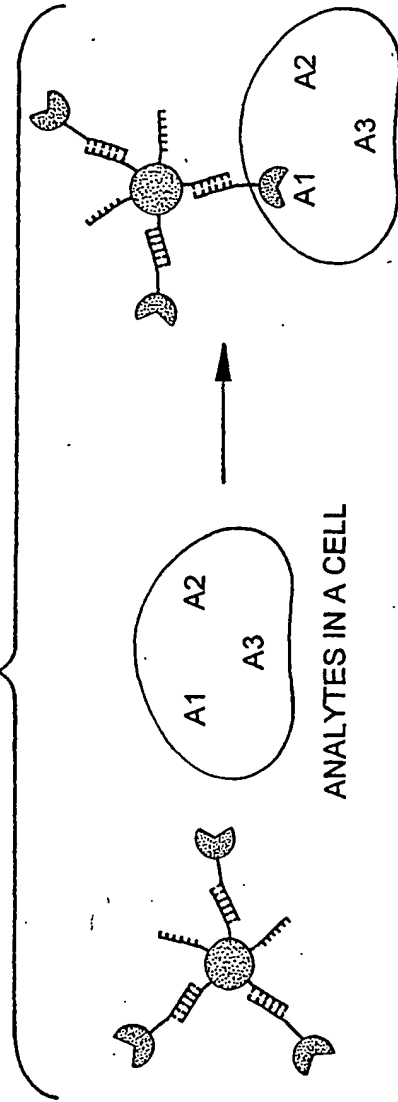


FIG. 50A

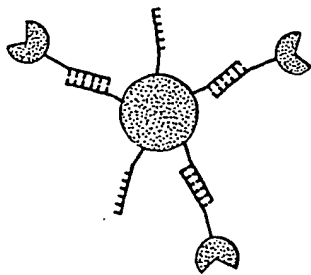


FIG. 50B

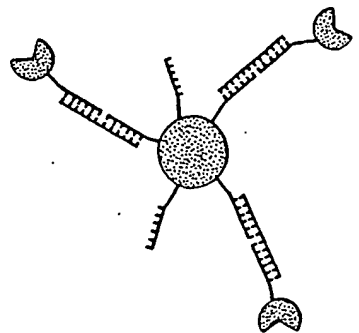
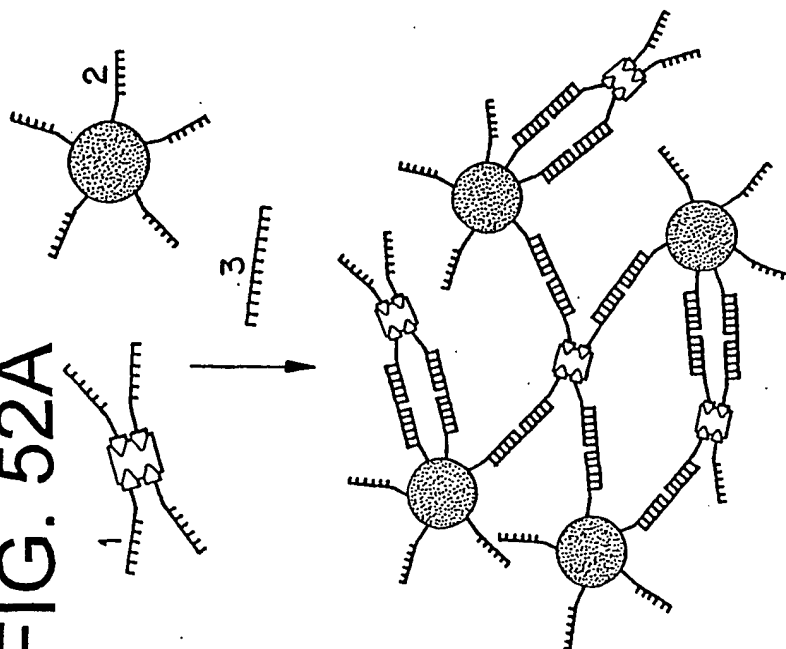


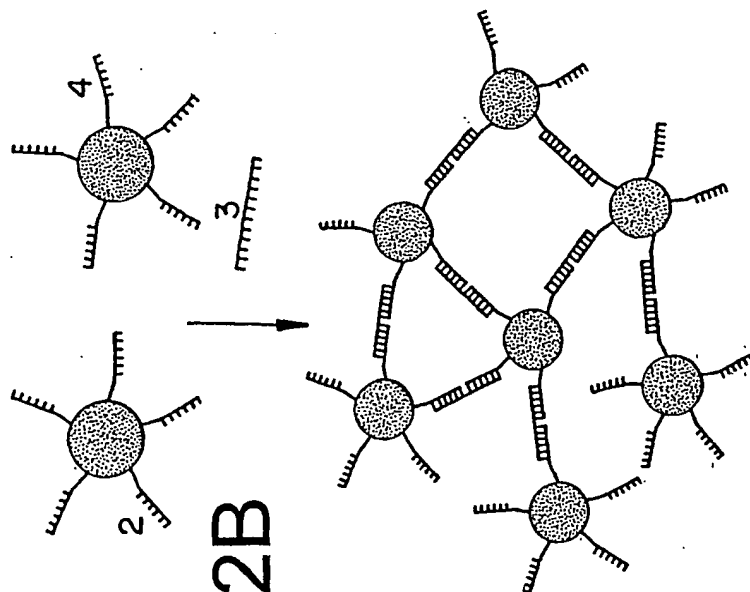
FIG. 52A



- 1 3' biotin-TEG-A<sub>10</sub>-ATG CTC AAC TCT 5' [SEQ. ID NO. 73]  
 2 5' SH(CH<sub>2</sub>)<sub>6</sub>-A<sub>10</sub>-CGC ATT CAG GAT 3' [SEQ. ID NO. 74]  
 3 5' TAC GAG TTG AGA ATC CTG AAT GCG 3' [SEQ. ID NO. 75]

● 13 nm Au NANOPARTICLES    [C] STREPTAVIDIN

FIG. 52B



- 2 5' SH(CH<sub>2</sub>)<sub>6</sub>-A<sub>10</sub>-CGC ATT CAG GAT 3'  
 3 5' TAC GAG TTG AGA ATC CTG AAT GCG 3'  
 4 3' SH(CH<sub>2</sub>)<sub>3</sub>-A<sub>10</sub>-ATG CTC AAC TCT 5'

● 13 nm Au NANOPARTICLES

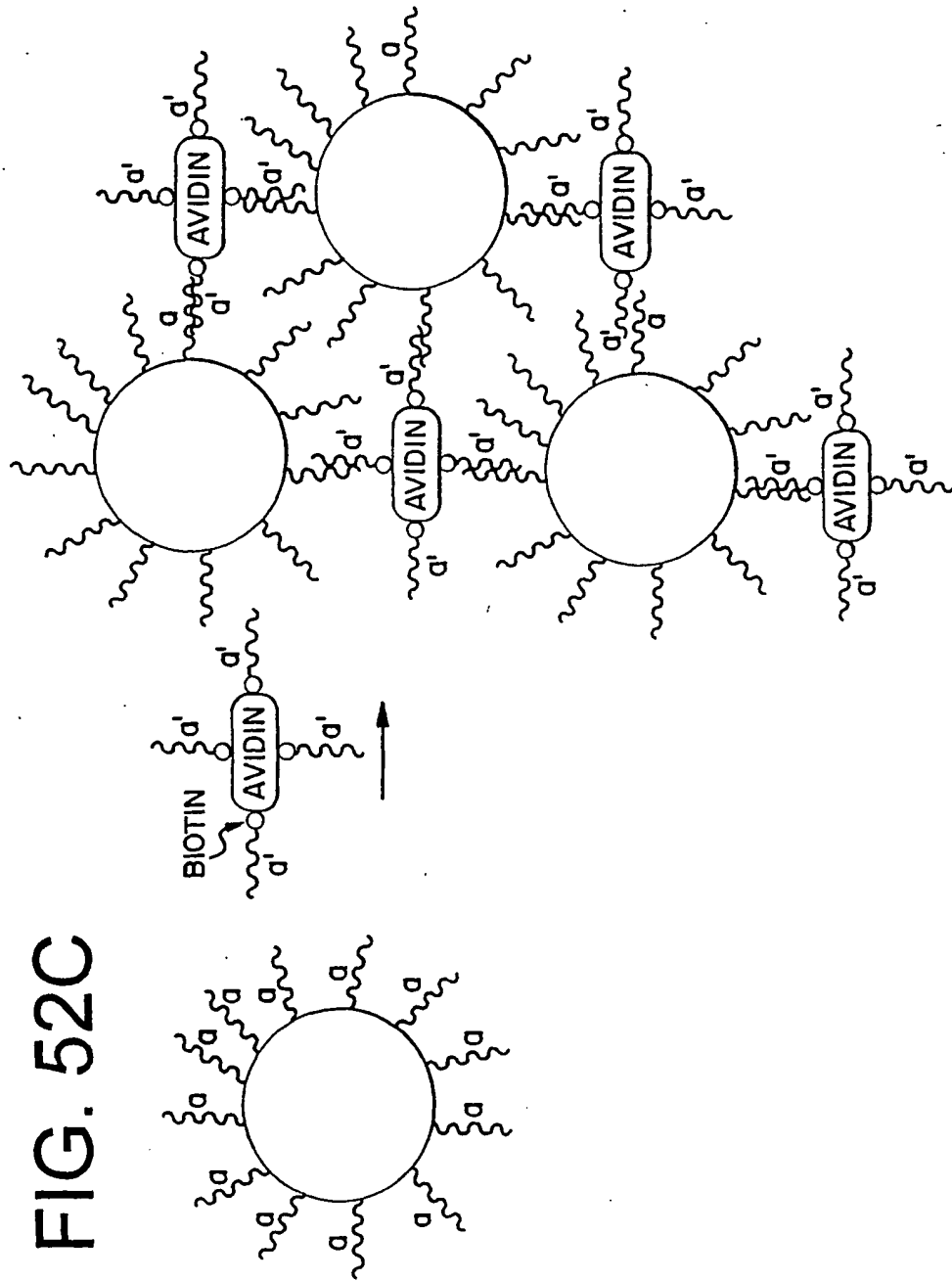


FIG. 52C

FIG. 53

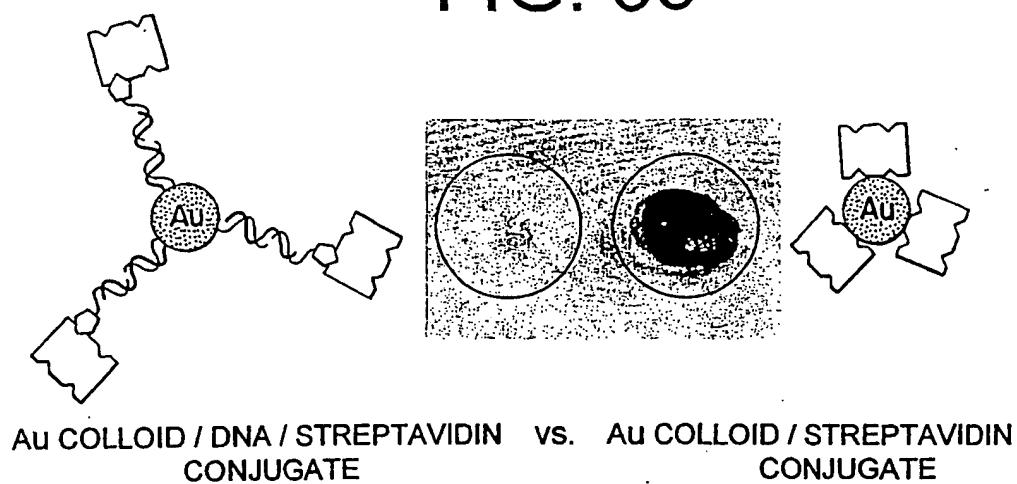


FIG. 54

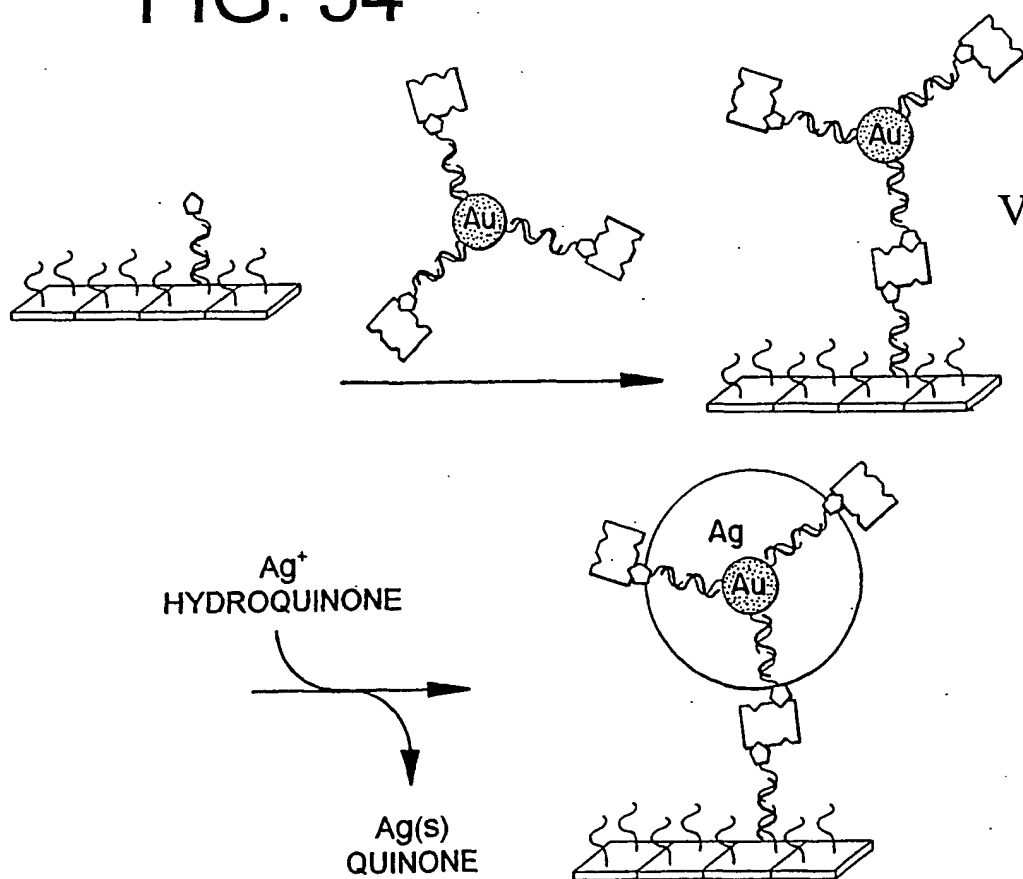


FIG. 58A

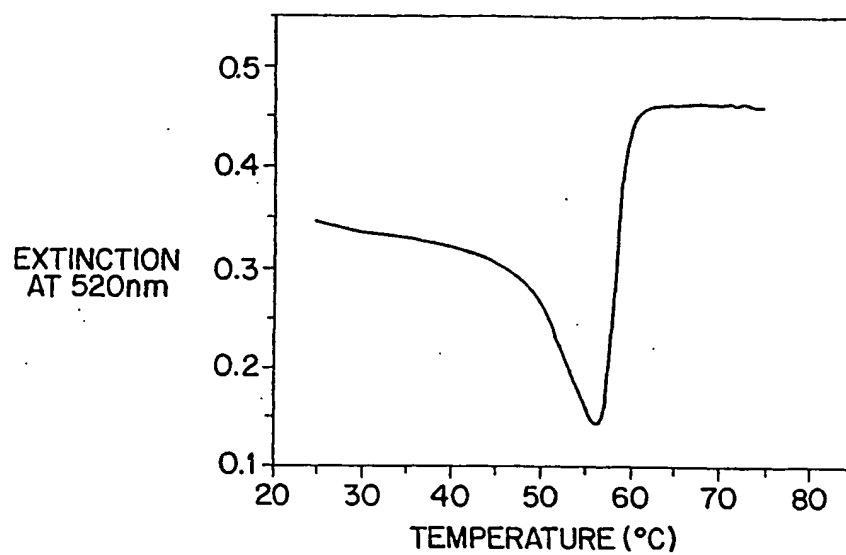


FIG. 58B

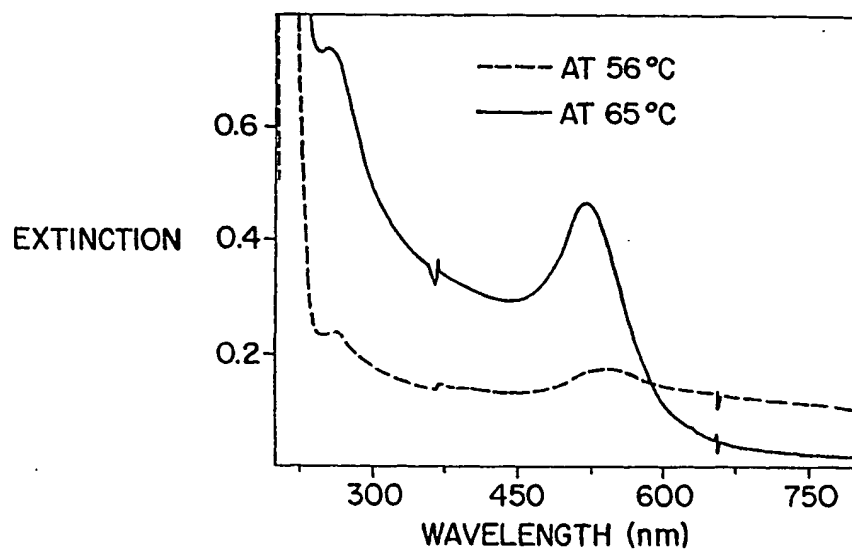


FIG. 59

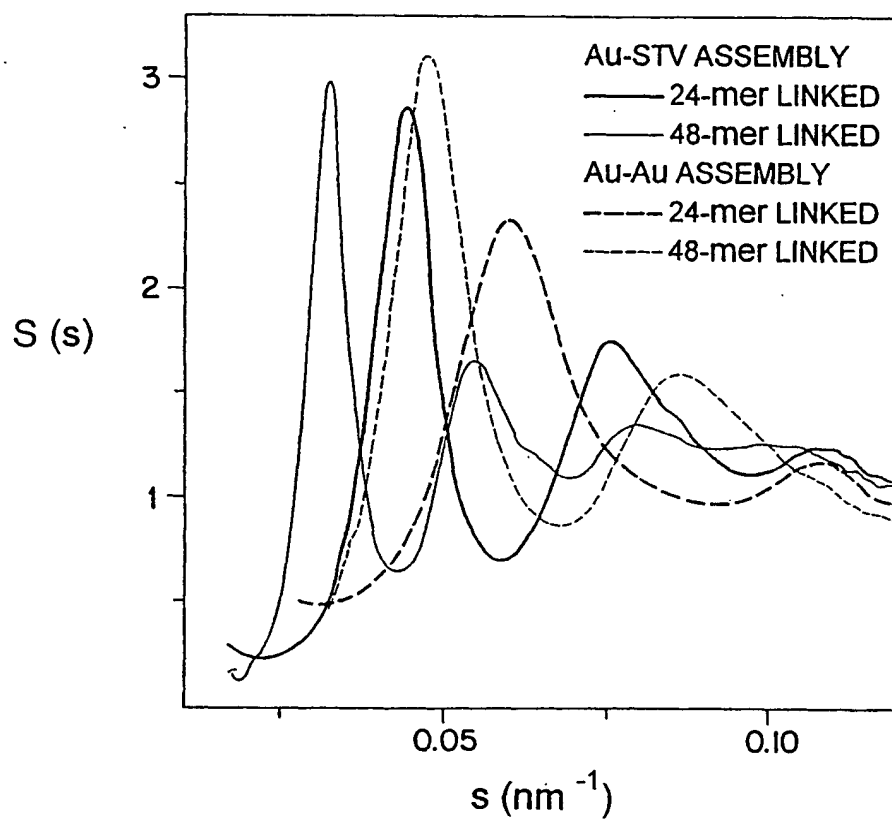


FIG. 60

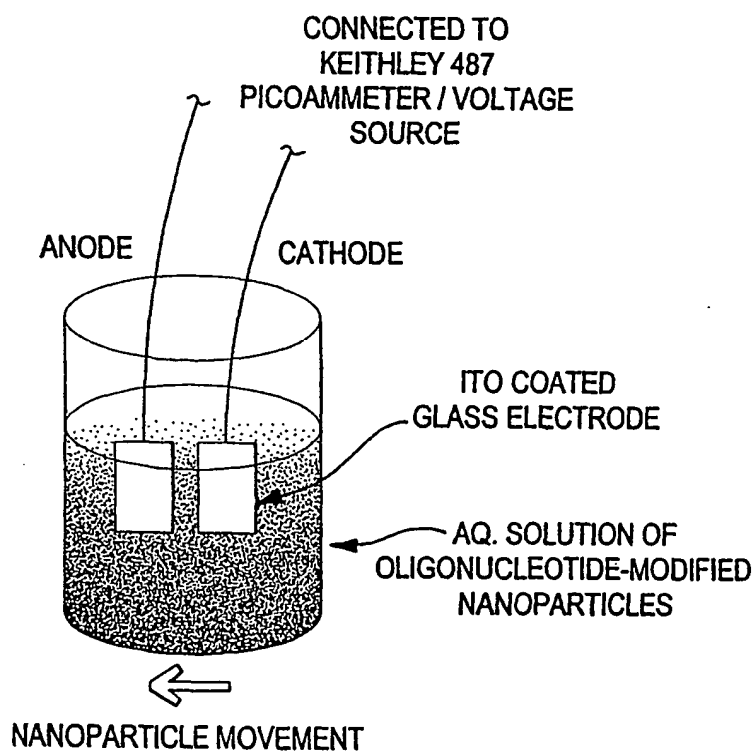
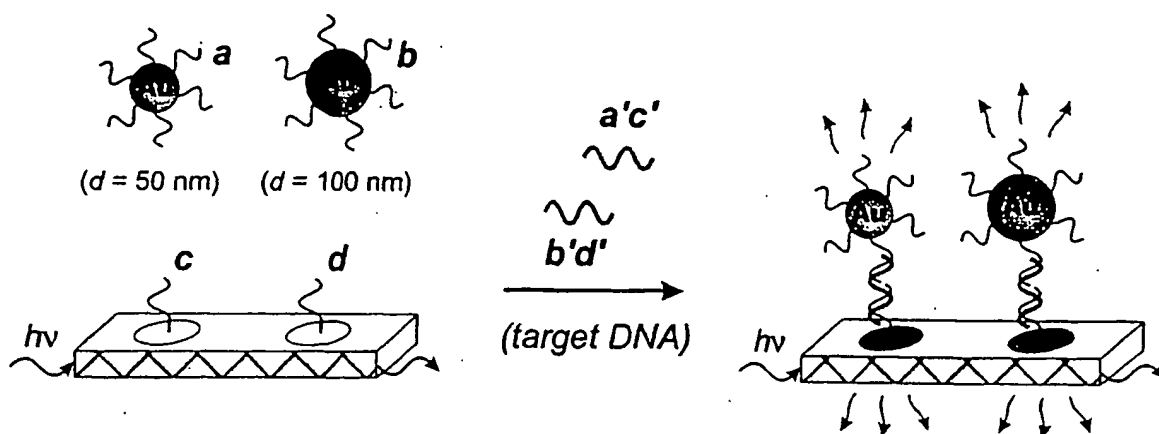
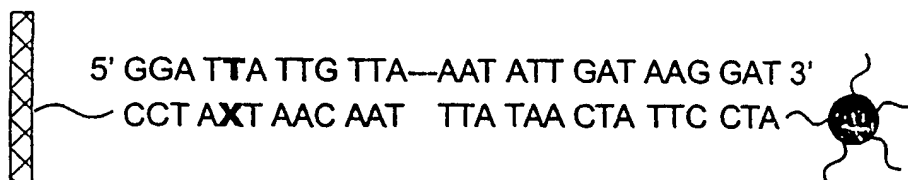


Figure 6)

**A****B**

**X** = A (complementary),  
G,C,T (mismatched)

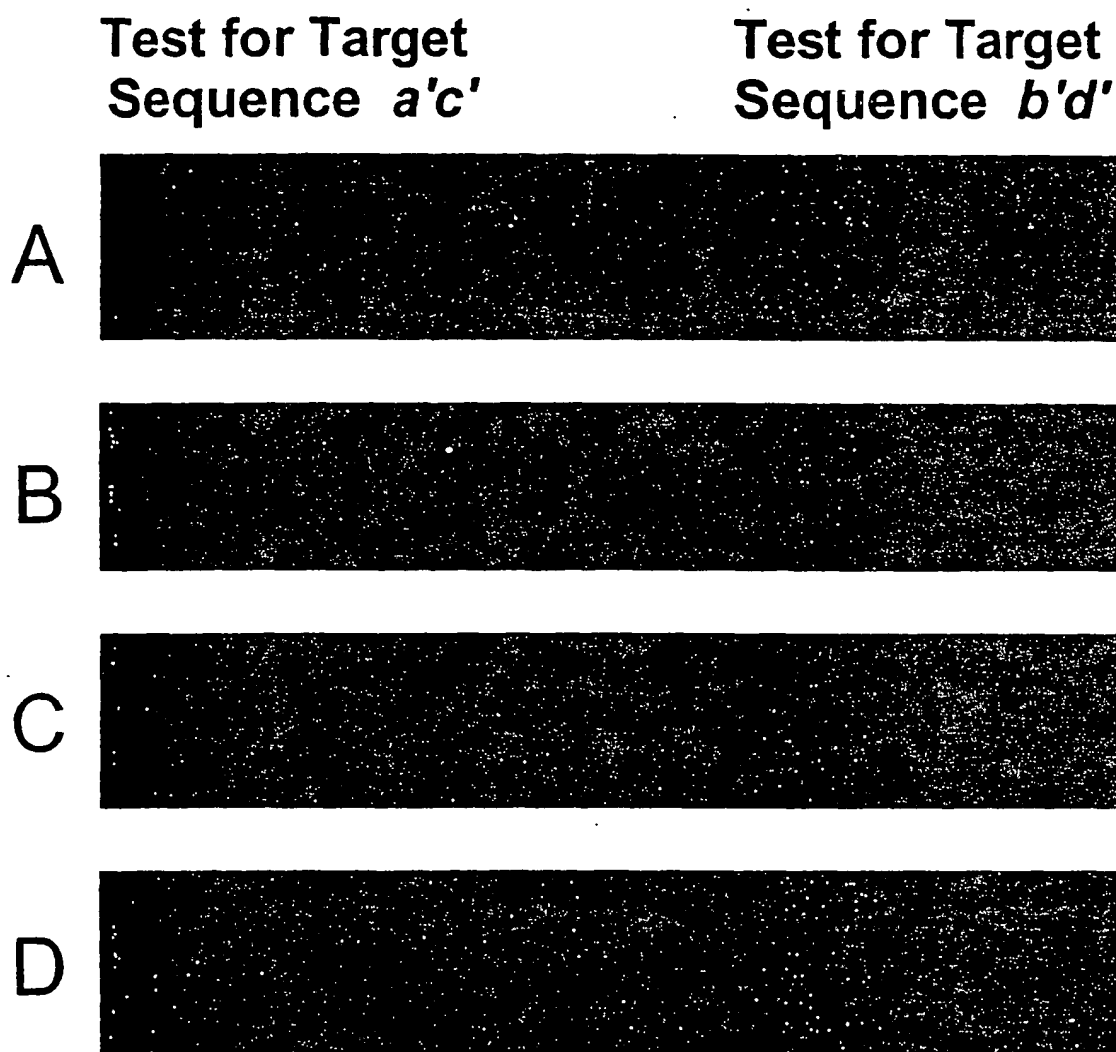
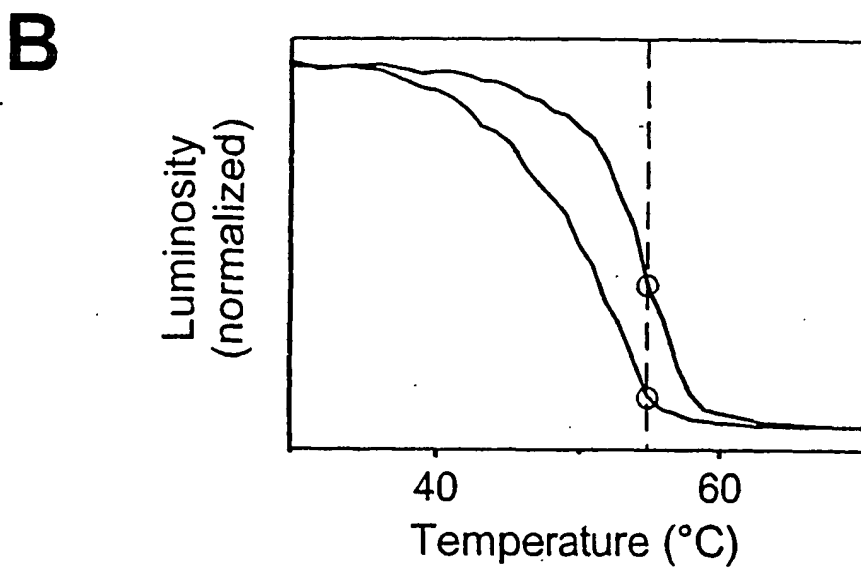
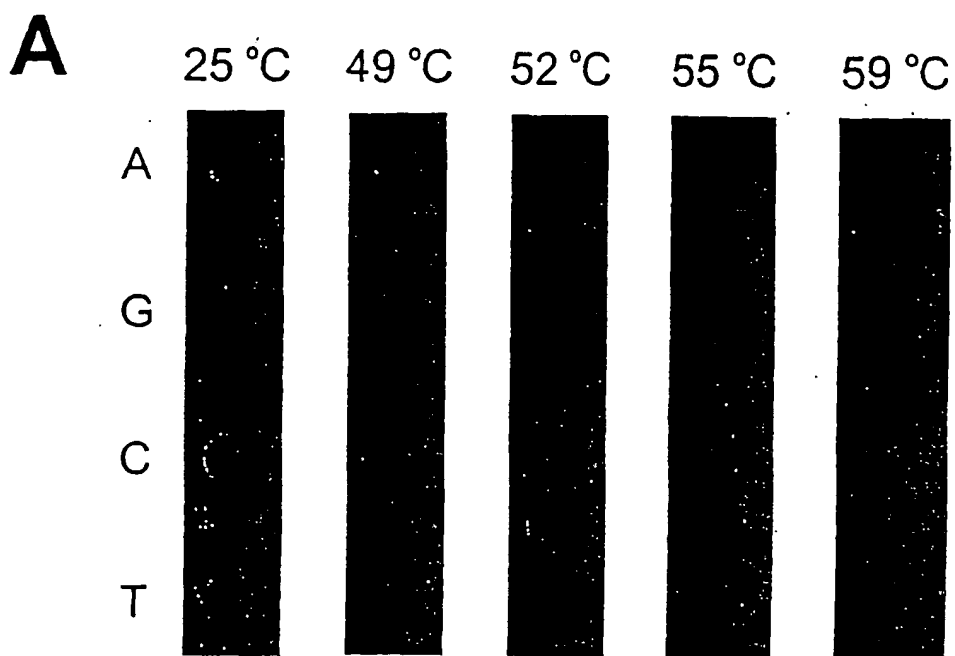


Figure 62

G. Lu, T. A. Taton and C. A. Mirkin



G. Lu, T. A. Taton and C. A. Mirkin

Figure 63

FIG. 55

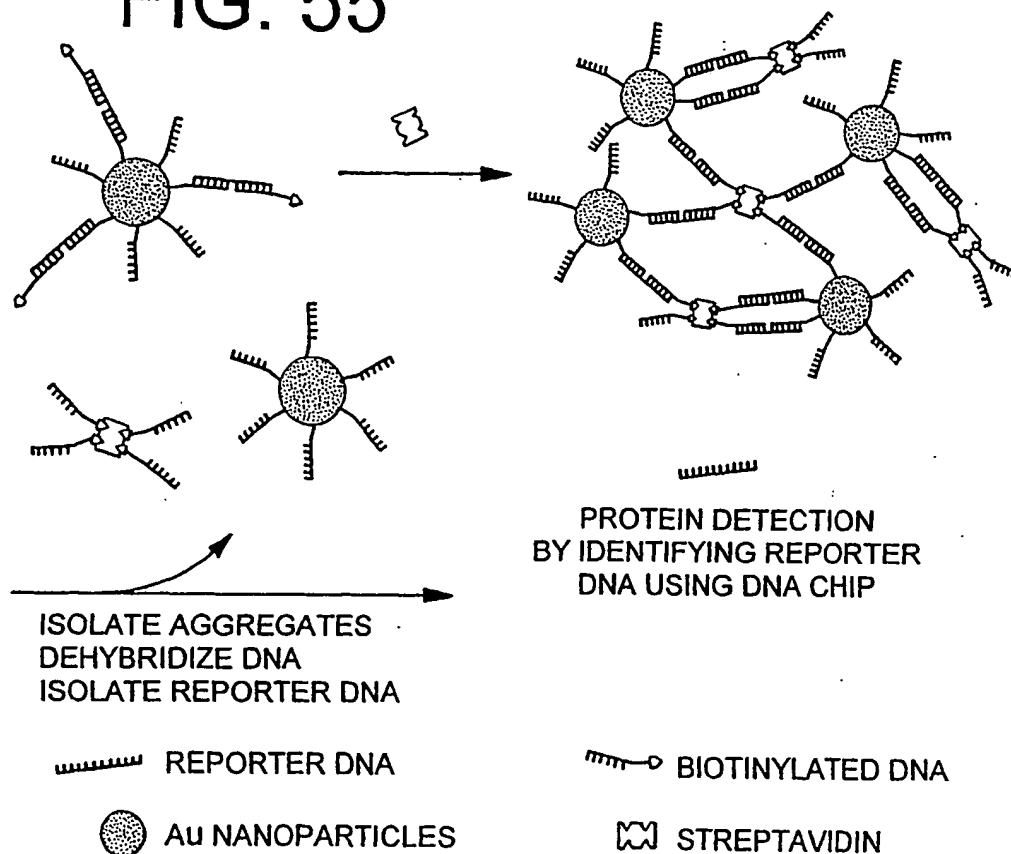


FIG. 56

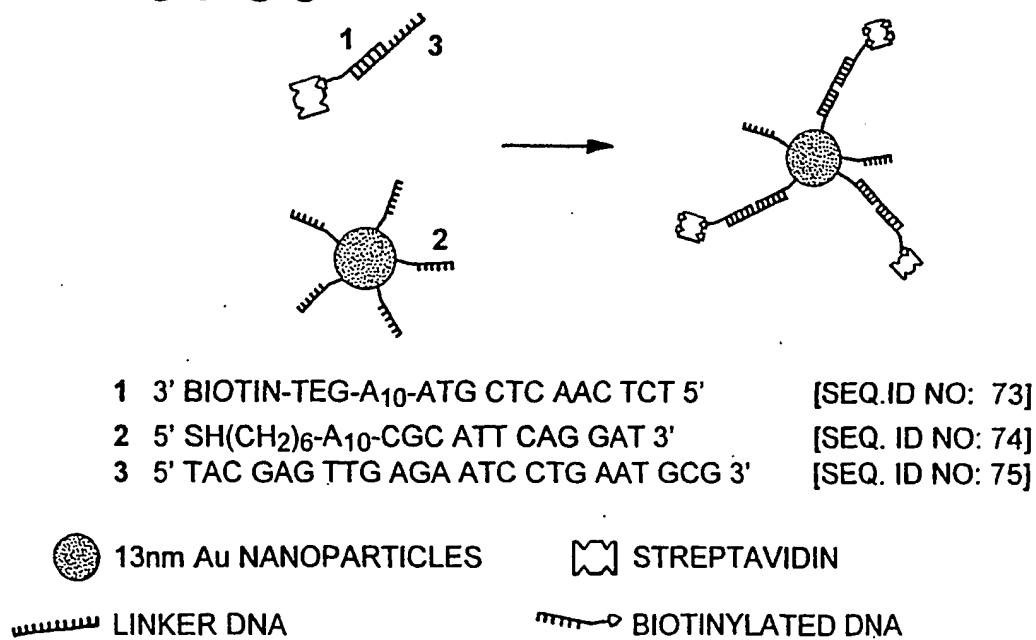


FIG. 57A

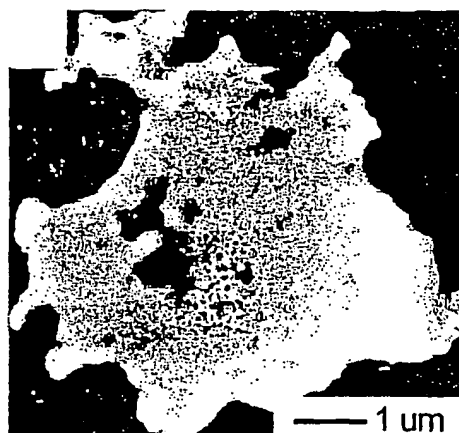


FIG. 57B

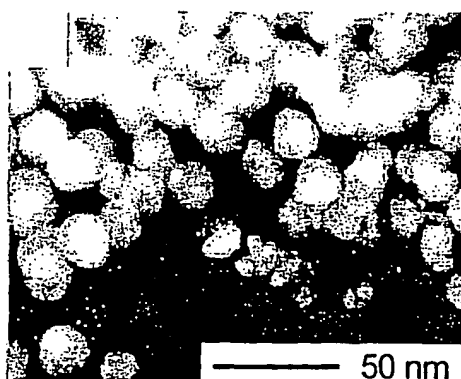


Figure 64

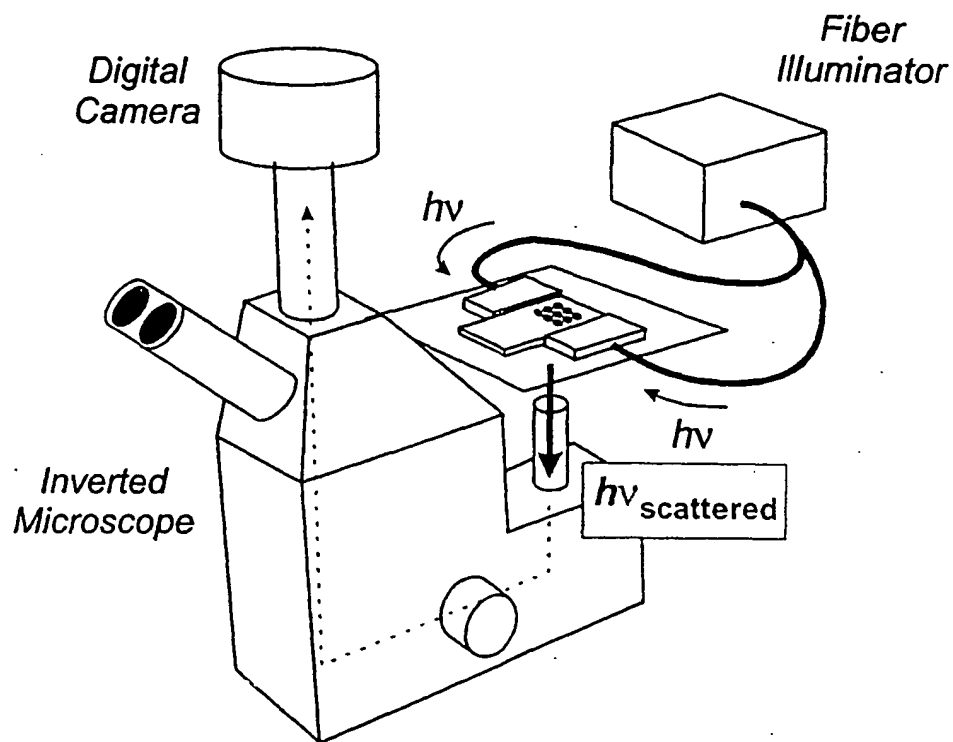
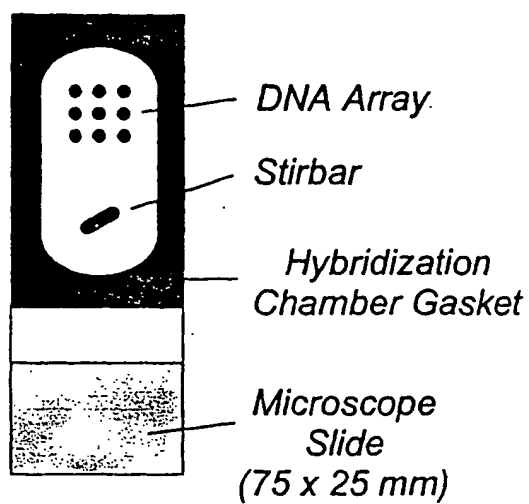
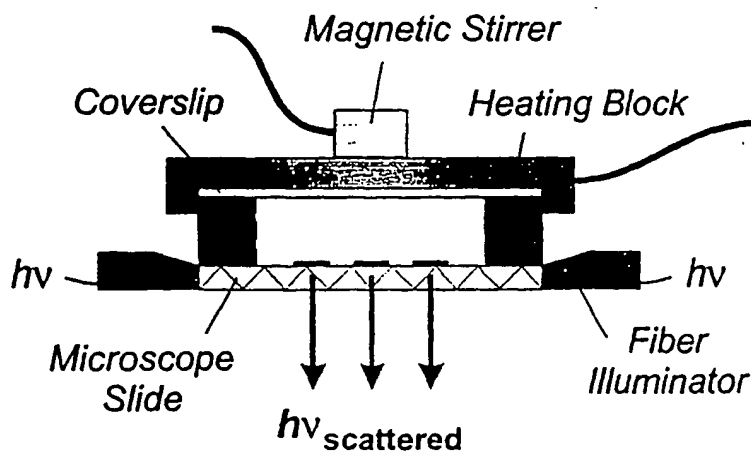


Figure 65

S9

**A****B**

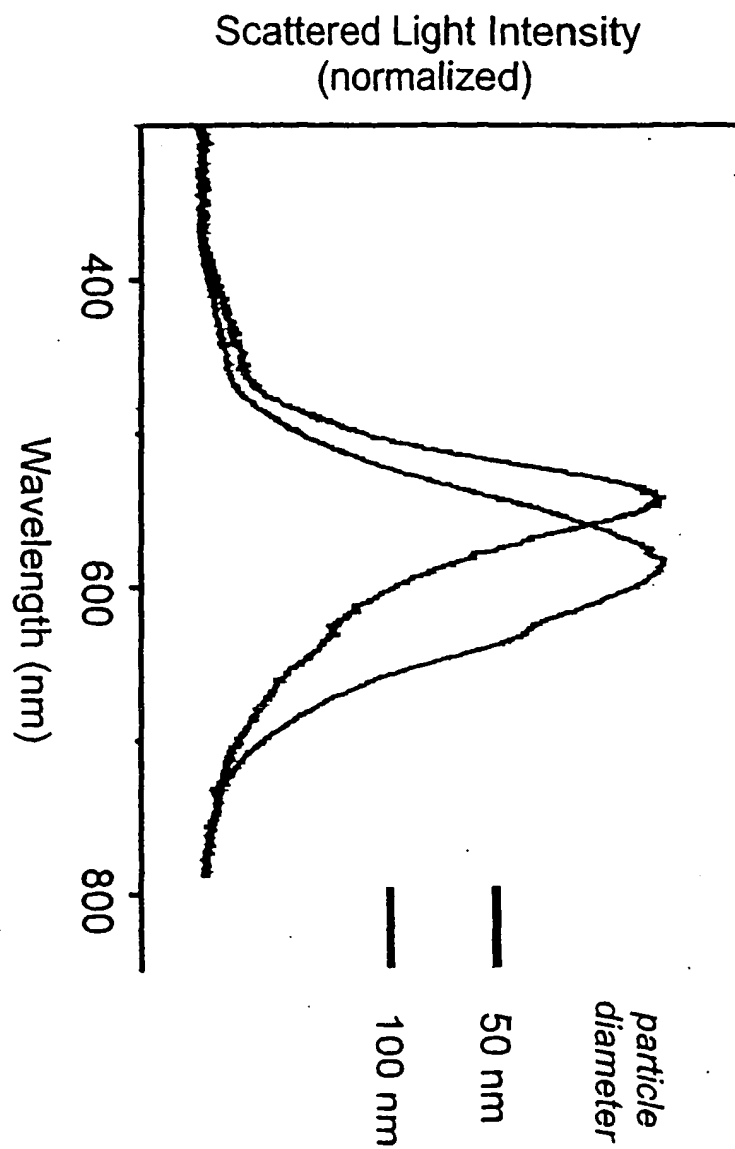
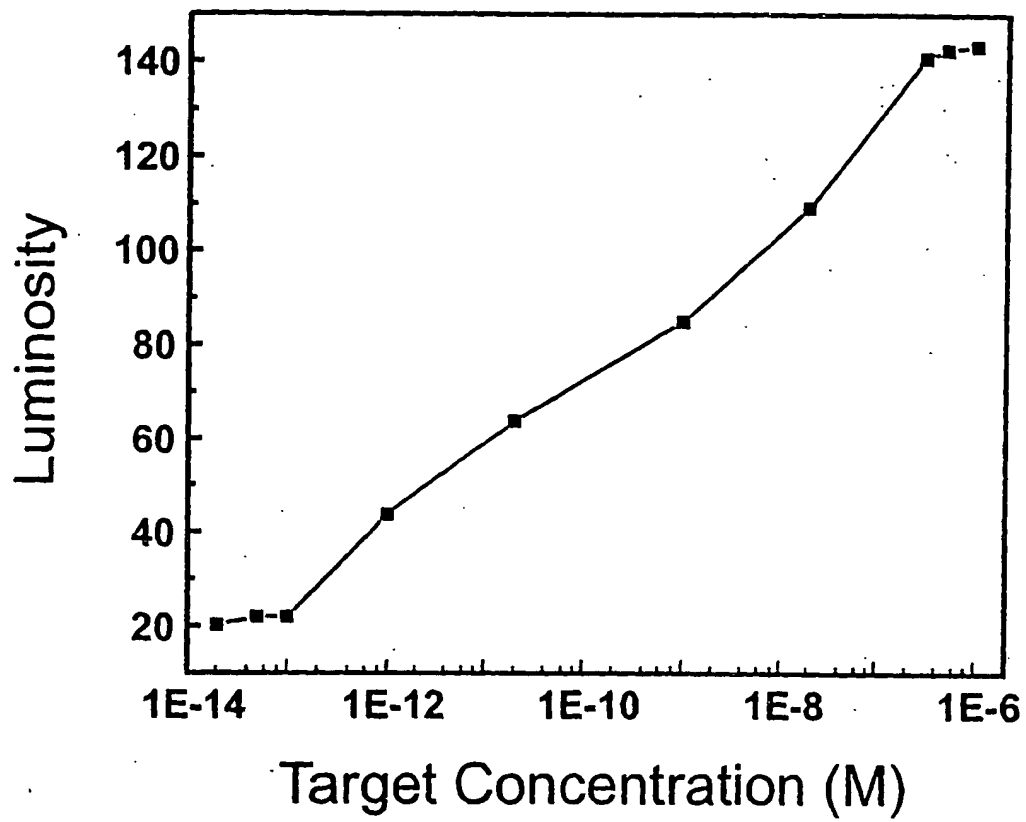


Figure 6b

*Figure 67*

## SEQUENCE LISTING

<110> Nanosphere, Inc.  
Mirkin, Chad A.  
Letsinger, Robert L.  
Mucic, Robert C.  
Storhoff, James J.  
Elghanian, Robert  
Taton, Thomas A.  
Garimella, Viswanadham  
Li, Zhi  
Park, So-Jung

<120> NANOPARTICLES HAVING OLIGONUCLEOTIDES ATTACHED THERETO  
AND USES THEREFOR

<130> 00-1272-D

<140> 09/927,777  
<141> 2001-08-10

<150> 09/820,279  
<151> 2001-03-28

<150> 09/760,500  
<151> 2001-01-12

<150> 60/254,392  
<151> 2000-12-08

<150> 60/254,418  
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<150> 60/282,640  
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synthetic sequence

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atggcaacta tacgcgctag

20

<210> 3

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<213> Artificial Sequence

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ccttgagatt tccctc

16

<210> 4

<211> 16

<212> DNA

<213> Artificial Sequence

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<400> 4

gagggaaatc tcaagg

16

<210> 5

<211> 18

<212> DNA

<213> Artificial Sequence

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synthetic sequence

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aacttgcgct aatggcga

18

<210> 6

<211> 26

<212> DNA

<213> Artificial Sequence

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<400> 6

aagttgcgct ttacggctaa tggcga

26

<210> 7

<211> 15

<212> DNA

<213> Artificial Sequence

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15

<210> 8  
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15

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15

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<211> 28  
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<400> 10  
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28

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<400> 11  
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28

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15

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<400> 13  
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30

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15

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30

<210> 16  
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<400> 16  
gtcgatagga aacgactcta gcgc

24

<210> 17  
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<210> 20  
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<210> 21  
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24

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23

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taggacttac gc 12

<210> 29  
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<210> 31  
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atcctgaatg cg 72

<210> 32  
<211> 48  
<212> DNA  
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<400> 32  
gttgccgta aagcgccaa tatatgcatg attgctcgt cttacgg 48

<210> 33  
<211> 12  
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synthetic sequence

<400> 33  
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<210> 34  
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<210> 35  
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<213> anthrax

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attattgtta aatattgata aggatataag aaaaatatta tccagggtta tattgtagaa 120  
attgaagata ctgaagggt t 141

<210> 37  
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<212> DNA  
<213> Artificial Sequence

<220>  
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## synthetic sequence

<400> 37  
taacaataat ccctc 15

<210> 38  
<211> 15  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:random  
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<400> 38  
atccttatca atatt 15

<210> 39  
<211> 30  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 39  
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<210> 40  
<211> 25  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

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tggtgacgaa ttaattactt ctcta 25

<210> 41  
<211> 27  
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## synthetic sequence

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<210> 44  
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aaaaaaaaaa cgcattcagg at 22

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## synthetic sequence

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aaaaaaaaaa cgcattcagg at 22

<210> 48  
<211> 24  
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<220>  
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synthetic sequence

<400> 48  
tacgagttga gaatcctgaa tgcg 24

<210> 49  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 49  
ctacttagat ccgagtgccc acat 24

<210> 50  
<211> 12  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 50  
cgcattcagg at 12

<210> 51  
<211> 32  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 51  
aaaaaaaaaa aaaaaaaaaa cgcattcagg at 32

<210> 52  
<211> 32  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:random

## synthetic sequence

<400> 52  
cgcatcagg atwwwwwww wwwwwwwww ww 32

<210> 53  
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<212> DNA  
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<220>  
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synthetic sequence

<400> 53  
atcctgaatg cg 12

<210> 54  
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<220>  
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synthetic sequence

<400> 54  
atcctgaatg cg 12

<210> 55  
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<220>  
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synthetic sequence

<400> 55  
aaaaaaaaa aaaaaaaaaa 20

<210> 56  
<211> 27  
<212> DNA  
<213> Anthrax

<400> 56  
ggattattgt taattattga taaggat 27

<210> 57  
<211> 12  
<212> DNA  
<213> Anthrax

<400> 57  
taacaatnat cc 12

<210> 58  
<211> 15

<212> DNA  
<213> Anthrax

<400> 58  
atccttatca atatt

15

<210> 59  
<211> 12  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 59  
tctcaactcg ta

12

<210> 60  
<211> 24  
<212> DNA  
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<220>  
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synthetic sequence

<400> 60  
tacgagttga gaatcctgaa tgcg

24

<210> 61  
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<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 61  
gcgtaagtcc taacgtacta acggagcaga attgccagag ttgagcat

48

<210> 62  
<211> 72  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 62  
gcgtaagtcc tacaacaggc atttcgcagg ttatatacgt actaacggag cagaattgcc 60  
agagttgagc at 72

<210> 63  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 63  
tgcattgattg cctcgtctta acgg 24

<210> 64  
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<212> DNA  
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<220>  
<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 64  
gttgctccgta aagcgtccaa tatatgcatg attgcctcgt cttaacgg 48

<210> 65  
<211> 16  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 65  
tatcgttcca tcagct 16

<210> 66  
<211> 15  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 66  
ttgatcttcc gttct 15

<210> 67  
<211> 34  
<212> DNA  
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<220>  
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synthetic sequence

<400> 67  
agaacggaaa gatcaacgag ctgatggaac gata 34

<210> 68  
<211> 30  
<212> DNA  
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<220>  
<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 68  
aaaaaaaaaa aaaaaaaaaa gcagacctca 30

<210> 69  
<211> 31  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 69  
aaaaaaaaaa aaaaaaaaaa cctatgtgtc g 31

<210> 70  
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<212> DNA  
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synthetic sequence

<400> 70  
aaaaaaaaaa aaaaaaaaaa 20

<210> 71  
<211> 21  
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<220>  
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synthetic sequence

<400> 71  
cgacacatag gtgaggtctg c 21

<210> 72  
<211> 35  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 72  
aaaaaaaaaa aaaaaaaaaa atccttatca atatt 35

<210> 73  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 73  
tctcaactcg taaaaaaaaa aa 22

<210> 74

<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 74  
aaaaaaaaaa cgcattcagg at 22

<210> 75  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
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synthetic sequence

<400> 75  
aaaaaaaaaa cgcattcagg at 22

<210> 76  
<211> 24  
<212> DNA  
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<220>  
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synthetic sequence

<400> 76  
tacgagttga gaatcctgat tgcg 24

<210> 77  
<211> 35  
<212> DNA  
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<220>  
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synthetic sequence

<400> 7  
aaaaaaaaaa atccttatca atatt 35

<210> 78  
<211> 35  
<212> DNA  
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synthetic sequence

<400> 78  
aaaaaaaaaa taacaataat ccctc 35

<210> 79  
<211> 35  
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<220>

<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 79

taatatcctt cttataaaaa aaaaaaaaaa aaaaa

35

<210> 80

<211> 35

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 80

ctacaatata accctaataa aaaaaaaaaa aaaaa

35

<210> 81

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 81

ataagaagga tattaaatat tgataaggat

30

<210> 82

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:random  
synthetic sequence

<400> 82

agggttatat tgtaggaggg attattgtta

30

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